The Yale Journal of Biology and Medicine

The GROVER FRANCIS POWERS *Number*

Vol. 24, No. 4 *February, 1952* *New Haven, Conn.*

Scope. THE YALE JOURNAL OF BIOLOGY AND MEDICINE publishes original contributions in all fields of medicine, the fields of biology that are related to medicine, and in the history and teaching of these subjects.

Mailing address. Manuscripts should be addressed to THE YALE JOURNAL OF BIOLOGY AND MEDICINE, 333 Cedar Street, New Haven 11, Connecticut, U.S.A. All manuscripts should be mailed flat.

Preparation of copy. Papers should be typed in double or triple space, with references typed in double space on a separate sheet. For the convenience of authors, as well as of the editors, certain conventions in style of citation have been adopted, as follows: References will be listed alphabetically by author and numbered consecutively. In the text they will be cited by superior number without parentheses. The order of citation of journal articles will be: author's name (surname followed by initials or forename if there is no middle initial), title of article, abbreviated title of journal, year, volume number, and first page of article. Titles of journals will be abbreviated in accordance with the style used in the *Index-Catalogue of the Surgeon General's Office.* (In case the Index-Catalogue is not available to an author, full titles of journals should be submitted without abbreviation.) References to books will include the author's name, the title of the book, and the place of publication, publisher, and date, followed by the page or pages containing the information to which reference is made. Authors of historical papers may use the conventional footnote style.

Rieser, Willy and Rieser, S. L.: The etiology of orthostatic albuminuria. J. Am. M. Ass., 1922, *78*, 644.

Barcroft, Joseph: *The respiratory function of the blood.* Cambridge, Cambridge University Press, 1914, pp. 58-61.

Illustrations. All illustrations and tabular matter must be in finished form for the printer; they will usually be reduced for printing to 4 inches or less in width. The artist should be informed of the anticipated reduction before the drawing is made. All illustrative material should have titles, and the legends should be on the material itself as well as typed on a separate sheet.

Each paper is accepted with the understanding that it is to be published exclusively in THE YALE JOURNAL OF BIOLOGY AND MEDICINE unless some other specific arrangement has been made in advance.

Costs chargeable to authors. The number of free illustrations will vary with the length of the paper, but usually only two pages of halftones will be allowed free. Costs for additional halftones will be charged to the author. Special typography, including tables and formulas, in excess of 10 per cent of composition costs are chargeable to the author. Corrections in galley proof in excess of 5 per cent of original composition costs will also be charged to the author. Page proof will not normally be sent to the author, but in the event that an author makes any changes from copy after galley proof has been submitted, the entire cost will be charged to him.

Subscriptions. THE YALE JOURNAL OF BIOLOGY AND MEDICINE is published in September, November, December, February, April, and June from 333 Cedar Street, New Haven 11, Connecticut, U.S.A. The subscription price for one volume of six issues is $6.00 in the United States, $7.50 in other countries. For students registered in any school of Yale University, the subscription price is $4.00 per volume. A subscription is included with dues ($6.00) to the Association of Yale Alumni in Medicine. Single copies are $1.50 each except for special issues.

Entered as second-class matter January 11, 1929, at the post office at New Haven, Connecticut, under the Act of March 3, 1879.

Copyright 1952 by THE YALE JOURNAL OF BIOLOGY AND MEDICINE, INC.

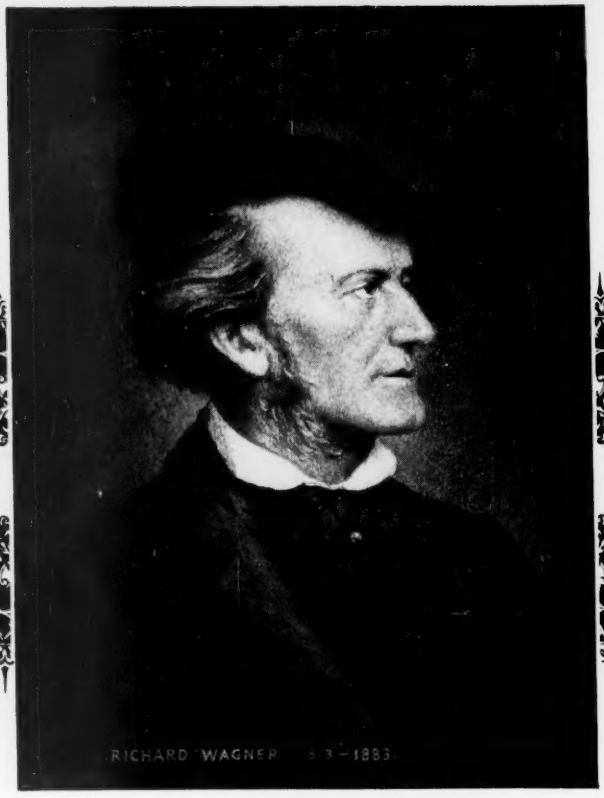
PRINTED BY THE VAN DYCK PRINTING CO., NEW HAVEN, CONN.

The Yale Journal of Biology and Medicine

The GROVER FRANCIS POWERS *Number*

February, 1952

Volume 24 Number 4



Psychoneurotics of Genius

Psychoneurotic traits — unbalanced emotional reactions, moods, ill temper and irresponsibility — are not uncommon among men of genius. Richard Wagner, great dramatic composer, had the emotional stability of a six-year-old throughout his adult life.

In many instances mild sedation has to be provided before a person of psychoneurotic make-up can achieve emotional stability. Mebaral combines a high degree of sedative effectiveness with a relative freedom from side effects such as languor and drowsiness. Patients usually become calmer, more cheerful and better adjusted to their surroundings without clouding of mental faculties. Average sedative dose: Adults, 32 mg. to 0.1 Gm. (½ to 1½ grains) three or four times daily. Children, 16 to 32 mg. (¼ to ½ grain) three or four times daily. Tablets ½, 1½ and 3 grains.

MEBARAL®

Brand of Mephobarbital

***Tasteless* SEDATIVE AND ANTIEPILEPTIC**
Little or No Drowsiness

WINTHROP-STEARNS INC. • NEW YORK 18, N. Y. • WINDSOR, ONT.

Mebaral, trademark reg. U. S. & Canada

TABLE OF CONTENTS

Grover Francis Powers and Pediatrics at Yale—

DANIEL C. DARROW, *Professor of Pediatrics, Yale University School of Medicine* 243

The Laboratory and the Community in the Undergraduate Training of a Physician—

JOHN McK. MITCHELL, *Dean, School of Medicine, University of Pennsylvania, Philadelphia* 252

Congenital Idiocy, Sexual Infantilism, and Dwarfism. A Clinical Report of Two Cases with Autopsy in One Case—

CLIFFORD JOSEPH, *Torrington, Connecticut*, and HERMAN YANNET, *Associate Clinical Professor of Pediatrics, Yale University School of Medicine; Medical Director, Southbury Training School, Southbury, Connecticut* 257

Self-Regulatory Feeding in a Premature Nursery—

FRANK H. HORTON, *Resident in Pediatrics*, LULA O. LUBCHENCO, *Instructor in Pediatrics*, and HARRY H. GORDON, *Professor of Pediatrics, University of Colorado School of Medicine, Denver* 263

Vitamin D and Citrate Metabolism: Studies on Rachitic Infants—

HAROLD E. HARRISON, *Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Pediatrician-in-Chief, Baltimore City Hospital*, and HELEN C. HARRISON, *Assistant in Pediatrics, Johns Hopkins University School of Medicine* 273

Variations in the Gag, Cough, and Swallow Reflexes and Tone of the Vocal Cords as Determined by Direct Laryngoscopy in Newborn Infants—

HERBERT C. MILLER, *Professor of Pediatrics*, G. O'NEIL PROUD, *Professor of Otorhinolaryngology*, and FRANKLIN C. BEHRLE, *Instructor in Pediatrics, University of Kansas Medical Center, Kansas City* 284

Studies in Congenital Cardiovascular Disease. IV. Impaired Pulmonary Diffusion of Oxygen in Persons with Left-to-Right Shunts—

NELSON K. ORDWAY, *Associate Professor of Pediatrics, Louisiana State University School of Medicine, New Orleans* 292

NOW

palatable
penicillin therapy
with

***concentrated** convenience for infants*

Pen-Drops*

100,000 units Potassium Penicillin G per cc.

highly concentrated oral penicillin liquid

bottles of 10 cc.

***elixir-ease** for children and adults*

Liquapen*

250,000 units Potassium Penicillin G per teaspoonful (5 cc.)

effective dosage: 2 teaspoonfuls
3 or 4 times daily—permits normal eating and sleeping schedules

bottles of 50 cc.

***readily accepted** by all patients—avoids the discomforts of parenteral therapy*

*Trademark

Antibiotic Division **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

Tuberculous Meningitis in Children. The Addition of Forty-one Proven Cases. A Critical Analysis of the Literature Dealing with Streptomycin Therapy since its Introduction—

ROBERT W. SAPPENFIELD, *Senior Assistant Surgeon (R) United States Public Health Service, Epidemic Intelligence Corps, New Orleans,* VERNE G. ROBINSON, *Director of the Division of Public Health Statistics, Indiana State Board of Health, Indianapolis,* and DWAIN N. WALCHER, *Assistant Professor of Pediatrics, Indiana University Medical Center, Indianapolis* 309

Passive Immunity to Vaccinia in Newborns. I. Placental Transmission of Antibodies—

C. HENRY KEMPE, *Assistant Professor of Pediatrics, University of California School of Medicine, San Francisco* 328

The Behavioural Response of Infants to Heat Stress—

ROBERT E. COOKE, *Assistant Professor of Pediatrics and Physiology; Markle Scholar in Medical Science, Yale University School of Medicine* 334

News and Comment

Department of Pediatrics 341

Bibliography of Grover F. Powers 342

Alumni Day Program 345

Events 347

Yale Alumni in Medicine (Alumni edition only) i

CONSULTING EDITORS

Francis G. Blake*
Joseph S. Fruton
Samuel C. Harvey
John S. Nicholas
Herbert Thoms
Milton C. Winternitz

* Died February 1, 1952.

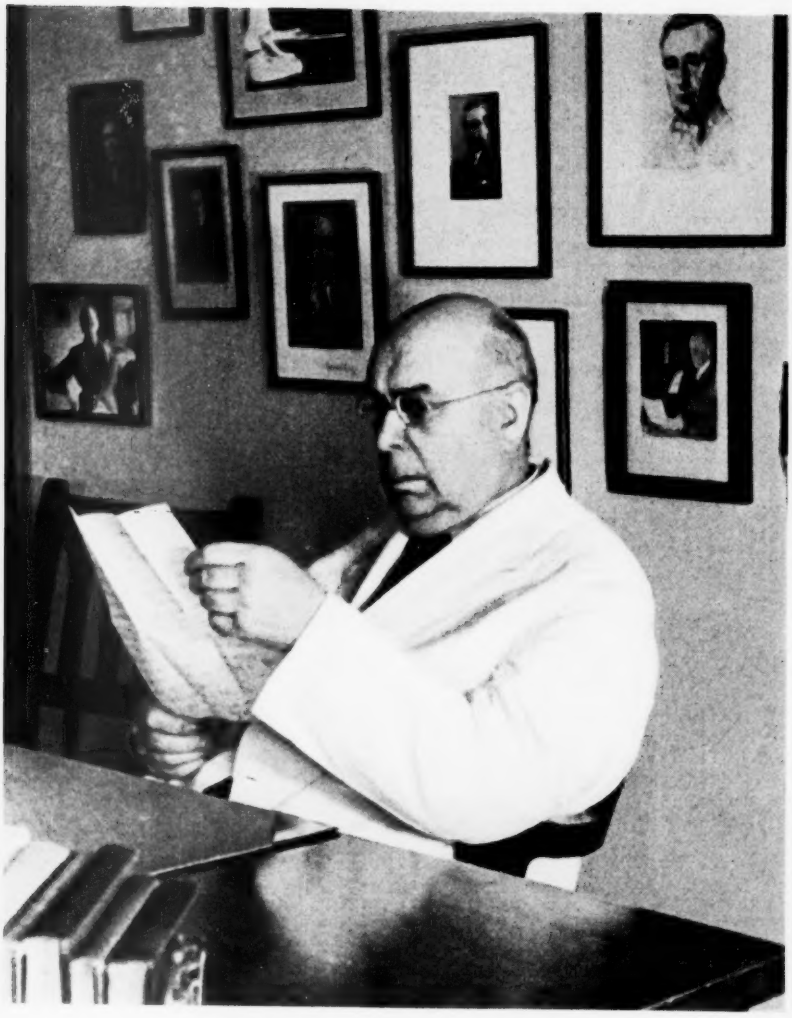
BOARD OF EDITORS

Edgar J. Boell
Victor M. Cutter, Jr.
John R. Brobeck, *Editor*
J. Roswell Gallagher
Alumni Editor
Frederick G. Kilgour
Managing Editor
Gerald Klatskin
Averill A. Liebow
George H. Smith
Editor-in-Chief Emeritus
Max Taffel
Elizabeth H. Thomson
Assistant Editor

Robert C. Cooke (*for this issue*)

ASSOCIATE EDITORS

Kenneth G. Bartels
Arthur C. Crovatto
Jack Peter Green
Virginia S. Green
Ralph Gross
Robert R. L. Guillard
Nicholas A. Halasz
Ora L. Kingsley
Wilbur P. McNulty, Jr.
Jacques M. Quen
Raymond Rappaport, Jr.
John Keith Rose
John F. Snyder
William F. Stephenson



GROVER FRANCIS POWERS

GROVER FRANCIS POWERS
AND
PEDIATRICS AT YALE

DANIEL C. DARROW*

This volume is affectionately dedicated to Grover F. Powers who, excepting for six months, worked in the Department of Pediatrics at Yale from 1921 until his retirement in 1951. The accompanying articles are, in a sense, a result of his leadership since they are all written by former house officers during these years. The following remarks will attempt to give those who do not know him some understanding of his influence. To those who know him, words will seem inadequate to convey the basis of this influence. Pediatrics at Yale will long be considered his creation and the measure of his life's work.

Grover F. Powers was graduated from Johns Hopkins in 1913 and served as intern, assistant resident, and pediatrician in charge of the dispensary until he came to New Haven. As director of the Babies' Milk Fund Association of Baltimore, he had experience in the preventive and public health aspects of pediatrics in the infant welfare clinics. During these, his formative years, Johns Hopkins was the foremost training center for pediatrics. One has only to recall the names of John Howland, James L. Gamble, Kenneth Blackfan, McKim Marriott, and Edward A. Parks to realize how outstanding were his friends. Of all this galaxy of stars, he became the greatest as pediatrician, as master of the science and art of caring for sick infants and children in the broadest sense. His life and work indicate what the pure pediatrician can do as a professor of pediatrics.

He brought to pediatrics a good mind which would have been equally successful in a number of fields. However, his spiritual attributes have provided guidance and motivation that have made his choice of pediatrics a particularly happy one. He is sensitive to changes in his environment to an almost unbelievable degree. President Conant, in illustrating the nature of scientific thought, points out that the initial observation that starts a chain of thought is often recorded merely in a phrase. In other words, some observer, often anonymous, calls attention to a change in a situation that might easily have passed unnoticed. I can well believe that this observer had the sensitiveness to which I refer. To most people, Powers' sensitiveness is most obvious in his ability to suffer and to feel the sufferings of others. Fundamentally, he is a man in whom no ambitions for himself have inter-

* Interne in Pediatrics, New Haven Hospital, 1922-1923.

fered with his judgment of a situation or of another person. For a man so sensitive, his objectivity has always astonished those who know him. He has the humility without which no man can rightly undertake to direct the lives of others. He once told me that as a boy he had prayed that he might have the courage to do what he thought was right. His prayer was answered, for in later life he always has had the courage to do what he thought was right but, as with all humble men, he has found it difficult to be sure that one *is* right. These qualities have made him not only a great pediatrician, but an ideal person to lead young men, for they instinctively know that he understands their problems and that there are no selfish motives behind his actions.

I shall make no attempt to divide the interests and activities of Grover F. Powers. His has been a life devoted in a unitary manner to the care of sick children. Although he has made substantial contributions to scientific problems in pediatrics, these appear as almost incidental by-products of the care of sick children and have often not been published. As a teacher of pediatrics he has been so successful in arousing interest in pediatrics in students and in producing well-trained pediatricians in his house staff that the department has always had a reputation for teaching pediatrics which is far greater than can be measured by the size of the department. Here again, the instrument has been attention to the many phases of the care of sick children. He has fostered new developments at Yale, such as changes in nursing, the broadening of the scope of social work, and co-operation with other departments such as public health, surgery, and obstetrics. He has served the State in organizing the Southbury Training School for feeble-minded children. All these efforts have also centered around the care and prevention of illness in infants and children.

He has lived with his patients as few interns do, spending days and nights watching and worrying over sick infants and children. This intimate association with sick children has taught him how the individual infant or child reacts to disease and what part therapy plays in modifying the course of disease. I have seen his equal in the diagnosis of disease but not his equal in evaluating the effects of disease on a particular child or the effect of therapy in modifying the course of disease.

This quality can be illustrated by a story that McKim Marriott loved to tell. When Howland and Marriott were first observing the effects of sodium bicarbonate on the acidosis of infantile diarrhea and were elated over the striking improvement, Marriott found Powers looking sad and said: "Grover, why are you looking so gloomy; we have found a way to treat diarrhea." Powers replied, "Yes, I know, but seven babies died of diarrhea last night." Marriott said, "Come, now, you saw how much better they looked after the injections of sodium bicarbonate." Powers said, "I saw the improvement and you probably know what should be done for acidosis, but do you know what the babies need? The babies used to live seven hours and

they last only four now." Doctor Marriott added at the end of his story that Powers was absolutely right, for Howland and he were giving too much bicarbonate; the discovery of acidosis did not lead to any simple treatment of infantile diarrhea. All who have worked with Doctor Powers have received the benefit of his clinical judgment, for treatment and research in medicine cannot safely be isolated in the laboratory or in precise clinical observations which neglect the experience and judgment of a good physician.

When Park and Powers arrived in New Haven, they had to establish a pediatrics department where one had scarcely existed before. In the first years, their two names can hardly be separated. They rapidly organized a department which emphasized care for the patient, training of students and interns by direct, responsible, but supervised contact with the patient, and research in the laboratory and on the wards. At this time infectious diseases were still prevalent, and the wards were full of diphtheria, scarlet fever, and dysentery. Rickets was almost universal, and nutritional disturbances in the first year of life were common since artificial feeding was guided by no simple, rational principle. These patients stimulated Powers to use his clinical knowledge to solve some of their problems and to suggest suitable fields for research to his associates who had skills which he did not possess. Powers published a simple, straightforward analysis of the principles of infant feeding, pointing out that food should contain sufficient calories, minerals, vitamins, and water and that the composition of the food should provide certain proportions of the total caloric intake as protein, fat, and carbohydrate. He was disappointed that this simple analysis was not immediately appreciated since it ended the irrelevant arguments about concentrations and emphasized the importance of total caloric intake of a suitable mixture. Although these principles are generally accepted, and are confirmed by analyses of diets in the tropics and the Arctic, this paper should still be read by writers of textbooks for adult medicine as well as pediatrics since protein requirement is still customarily defined in terms of body weight rather than caloric requirement. From clinical observations he established over twenty-five years ago, a regimen for the care of premature infants that was practically as successful as the best of the currently accepted methods. Indeed, present practice follows his early precepts to a surprising degree. At the suggestion of Lafayette B. Mendel, he gave liver extract as a source of possible unidentified vitamins in celiac disease. Unfortunately, these observations were only read in a paper before the New England Pediatric Society. He was apparently reluctant to publish his experience because liver extract does not cure the fundamental disturbance. However, twenty-five years of experience with liver extract indicates that good nutrition and well-being are restored, though abdominal distension persists. As has long been known, most of the patients with celiac disease recover if nutrition can be maintained. Recent papers by other investigators

show the same results. Powers also continued other studies on rickets similar to those he had been carrying on in Baltimore. New Haven was one of the first cities practically to abolish rickets. While Park and Eliot were the chief instruments behind this demonstration of the practical efficacy of cod liver oil, Powers' knowledge of the methods of administering well-baby clinics was important. In 1949, he received the Borden Award for outstanding achievement in research on nutritional disturbances of infants and children.

In 1926, Powers published a description of his comprehensive plan for the treatment of infantile diarrhea. He introduced the use of transfusions and correctly stated that the indication for transfusions is shock and not anemia. He carefully analysed the effects of a number of therapeutic procedures and provided a combination that was as successful as any system until potassium was added to his regimen. Powers' paper can well be studied to illustrate how shrewd clinical observations can serve to establish a therapeutic program. He appreciated that the program for the treatment of diarrhea was not meeting the needs of every case and he did not deceive himself that progress could be made by more precise application of certain features of the therapy or by neglect of the lessons of the past.

When Powers became head of the Department of Pediatrics in 1927, James Trask was persuaded to take charge of studies in infectious diseases. Trask had had an excellent training in bacteriology and immunology while working on the adult medical service with Francis Blake. With his clinical insight, Powers guided the enthusiasm of Trask in his bacteriological and immunological studies. On the basis of his experience with adults, Trask expected much of antipneumococcal sera and scarlatinal antitoxin. Powers always remained somewhat skeptical of the advantages of pneumococcal sera—especially the first ones tried. Owing to the infrequency of cases with the intense toxic reaction seen in adults, Powers felt that the disadvantages of scarlatinal antitoxin usually offset the benefits in children. The invasive phase of streptococcal infections dominates the picture in children. Because of their different experiences, Powers and Trask both had their concepts of infectious disease broadened by their discussions; they could agree entirely that the same infectious agent produces a different reaction in infants and children from that seen in adults. I do not know whether Trask or Powers played the more important rôle in developing certain ideas about the influence of age and previous infections in explaining the differences in reactions to infection. I suggest that the interplay of two diverse talents was as inseparable as those creating the Gilbert and Sullivan operas except that there was mutual stimulation without a trace of jealousy or unfriendliness. They were the spirits who gave us the description of age and previous infections as the explanation of the different manifestations of streptococcal infections.

Trask's untimely death brought an end to similar studies in other infections. When the sulfonamides and antibiotics reduced the death rate from infectious diseases, research was diverted from these fundamental problems and it became the fashion to assume that infections were no longer a major problem in pediatrics. Yet any thoughtful pediatrician—and Powers more than anyone—knows that childhood is still the age when infections are the most frequent and when immunity is acquired. Powers firmly believes that the pediatrician and general practitioner must know how to protect children from permanent damage due to apparently minor infections and how immunity is acquired without danger. The present trend in the age incidence of poliomyelitis serves to illustrate the soundness of this view. Pediatrics will have to come back to the unfinished task of determining the factors explaining the reactions to infections at different ages.

I can briefly state some of the influence Powers had on chemical research during these years. The series of papers on the physiological disturbances in diphtheria by Yannet and me arose from Powers' statement that glucose is sometimes beneficial in toxic cases. The studies on deficit of extracellular electrolytes grew out of his asking me why hypodermoclyses of 5 per cent solutions of glucose were irritating and often made the children sick. The reason was fairly obvious to me, but Yannet and I were surprised at the magnitude of the physiological disturbances produced by intraperitoneal injections of isotonic solutions of glucose. Harrison's paper on the nitrogen and calcium balances of infants fed condensed milk was undertaken because Powers felt that, contrary to current reasoning, the protein intake of this food was adequate. The paper on acidosis produced by protein milk followed his statement that he did not understand why protein milk was not tolerated by young infants. The clinical judgment of Powers on the effect of bicarbonate in acidosis prevented me from pursuing the will-o-the-wisp of precise regulation of bicarbonate and pH in acidosis. He was firmly convinced that restoring the bicarbonate concentration of serum rapidly with large doses of sodium bicarbonate was dangerous. For this reason, I knew that there was something wrong with the prevalent concepts of the distribution of sodium and chloride in tissues and was driven to study intracellular fluids. It was the support of his clinical judgment that helped me feel sure that I was not deceiving myself when potassium produced an improvement in infantile diarrhea that we had not seen before. For myself I can say that no help is as much needed in laboratory and clinical research as the judgment of the course of disease that only a supreme clinician possesses.

When the new drugs decreased the mortality from infectious disease, the apparent emergence of psychological disturbances in pediatric practice brought nothing new to the attention of Powers. As was indicated by his encouragement of Doctors Putnam and Jackson, he has wanted psychiatric study and treatment as an integral part of pediatrics. The establishment of

a unit in which newborn infants are not separated from the mother has been another example of the mutual stimulation of two minds. This service has been particularly pleasing to him for it provides better care for the newborn and opportunities for accurate psychological observations. Ultimately, I believe he would have wanted to establish psychiatric care of children by pediatricians who would be willing to assume responsibility for somatic disorders while they made detailed psychiatric studies in selected cases in a manner analogous to the accepted practice for metabolic and infectious diseases. He is keenly sensitive to emotional disturbances of infants and children but, from his experience, he is afraid of any type of medical care that separates sick children from doctors who understand the reaction of infants and children to somatic disorders.

Because of his experience in the dispensary in Baltimore, Powers knew that the outpatient department was one of the most important means of training physicians for practice. Here the student and house officer saw the illnesses which constitute the major part of practice. However, it remained an incomplete experience since the illnesses treated in the dispensary may be seen in the home as well as in the office in practice. For various reasons not altogether under Powers' control, it has not been possible to include home visits as a part of dispensary training. However, for the newborn, he was able to include home visits. He has felt that the outpatient service is most valuable after the physician has become familiar with the complete picture of disease that is more readily obtained in the hospital. The defect in dispensary training worried Powers a good deal and for this reason he felt that it must be supplemented by an excellent service in the hospital. He has reasoned that the problems of practice that are not seen in the hospital can be adequately evaluated if the fundamentals of complete evaluation of cases have been properly mastered in the hospital. However, if the hospital training is neglected, there may never be opportunity to learn them in practice.

Powers tried to abolish the exhausting delays of the usual dispensary by an appointment system. For return visits, this was reasonably successful, but the rather sudden and unpredictable onset of illnesses in children made the appointment system unworkable for new cases. He found that it is impossible for men in practice to devote the necessary time to the routine dispensary work. For this reason, he persuaded practitioners to develop certain specialized aspects of the care of infants and children. He always felt the need of expert advice on hematology—an aspect of medicine not adequately represented at Yale. With this in mind, Tom Shaffer was sent to Boston for training in hematology and took charge of this work in the dispensary and the wards until he joined the Army. Fortunately, this work was later re-established by another trained hematologist when David Clement came to New Haven to practise pediatrics. Similarly, Morris Krosnick has developed studies in allergic diseases, Robert Salinger, heart

diseases, and Herman Yannet, neurological disorders. In order to assure excellent and consistent care of the patients, one of his best men who had more experience than the residents was kept in charge of the dispensary. The senior staff did not work regularly in the dispensary except as consultants because this would defeat the purpose of full-time medicine. He has felt that full-time medicine was established to permit certain men to devote their time to activities that are not exactly the same as those of men in practice.

With the development of cardiac surgery, the need for technical and research facilities in this field at Yale was obvious but it seemed as if it would be impossible to establish so expansive a service. Through cooperation with the State, an excellent organization for treatment and study of all types of heart disease was established under Ruth Whittemore. The diagnostic service has worked smoothly with the Department of Surgery. Through the skills of Harris Shumaker and William Glenn, even the most difficult cardiac surgery is available at Yale. Despite the newness of the laboratory, one of the men from this unit, Paul Lurie, has taken charge of similar work at the University of Indiana.

As has been indicated, Powers contributed much to solving certain problems presented to him by patients. Through his leadership, the department was organized so as to provide excellent medical care in all phases of pediatrics. Conferences were arranged for practitioners who wished to learn of recent progress in pediatrics. He was elected president of the American Pediatric Society and his advice is sought by leaders throughout the country. However, he will ultimately be judged by his ability to develop men. As a university professor his greatest satisfaction and achievement have been the training of students to become physicians, and house officers to become pediatricians. He realized that this is something which ultimately the men must do for themselves but, by example, he could show the direction their efforts should take.

His method of developing men is so personal that it cannot be described except as an atmosphere in which work is effectively directed toward this goal.* The spirit he has strived to create is presented in his "Remarks to undergraduate students of clinical medicine" (Yale Journal of Biology and

* Without verifying the positions of each man, the following statements indicate the activities of the men and women who have been members of the Department of Pediatrics at Yale from 1921 to 1951. Seventeen have become full professors of pediatrics and one each, professors of bacteriology, psychiatry, and physiology. Of these twenty, sixteen took all or part of their resident training at Yale and four were Fellows. In addition, an equal number are members of medical faculties of senior rank—associate professors devoting whole or part time to teaching and research—and two are deans of medical schools. The head of the Children's Bureau is a former resident, and at least five former residents are directors of important institutions which are engaged in research or specialized pediatric service but are not associated with universities. Most of the two hundred-odd men and women who have spent one or more years in resident training are practising pediatrics or are engaged in some phase of the care of infants and children. About two-thirds were graduated from Yale University School of Medicine.

Medicine, 1949, *23,* 109). His success is indicated by a large number of excellent pediatricians in all parts of the United States, by a number of professors of pediatrics and teachers in medical schools and, not the least, by a large number of surgeons, general practitioners, and men in other fields of medicine who regard him as their most inspiring teacher at Yale. It is probably no exaggeration to state that a higher proportion of Yale students have expressed an abiding interest in pediatrics than those from any other school.

Powers regards the internship as the crowning educational experience of physicians, and the following years on the house staff as the most important part of the training of men who want to become expert clinicians or intend to become teachers and investigators in clinical medicine. For this reason, the work of the house staff is organized with education of future physicians as the chief objective. His unusual gift for estimating the ability of men and women insured the selection of an excellent house staff. He preferred to take men and women immediately after graduation since it is difficult for those with previous experience as interns to enter enthusiastically into the spirit which he tried to create. He does not believe that seeing a great many patients is a rewarding experience at this stage of their education unless there is also conscientious and expert teaching and supervision. He has instilled into his house staff the idea that the work of a physician cannot be properly undertaken except as a responsible service to the patient and the community. He has no sympathy with men who evaluate each job by what they can get out of it for themselves. On the other hand, he has no sympathy with the utilization of the work of the intern as service to the community when it has no educational value. To him, the education of the intern is incomplete if it merely teaches the techniques of current practice. It must give physicians the basis for evaluating future developments and, for this reason, is best carried out in hospitals with adequate diagnostic facilities and where men are engaged in research. He believes that men in internships in which they are rotated for short periods of time through a number of different services are working with a great handicap. The intern hardly has time to absorb the spirit of any medical discipline. Powers has not regarded development of pediatricians as the only function of his service, since he has taken a number of men who frankly stated that they wished to go into surgery or general practice. He has always studied the men continually and helped them to find a field of interest or a job which was suited to their capabilities. He varied the program of the second and third years on the house staff, emphasizing, for different men, research or various phases of practice.

Powers regards visiting rounds as a trust, not only to the patients but to the house staff. He does not believe this trust can be fulfilled by anyone who is unwilling or unable regularly to devote the necessary time to the details of diagnosis and treatment or who has not the background to know by

experience the problems which must be met. He believes that the time that an intern spends on the wards is so essential to his education that the supervision on rounds should be as expert and consistent as possible.

For Powers, the relationship of the attending physician to the house staff is one of consultation, first, on the needs of the patient, and second, on the educational needs of the intern. Nothing must interfere with this relationship. He found that the presence of more than two or three students or visiting doctors did interfere with the relationship. The rounds under these circumstances are likely to be conducted with reference to the students, or the visiting doctors, or the house staff. In any case, they cannot be made to fit the needs of diverse groups. He never conducted what has been called "grand rounds" on the wards. He would not deny that some people can make a different type of rounds an effective educational experience, but for him the relationship had to be a personal consultation between himself and the men who were taking care of the patients.

As the years pass, former students, house officers, and associates probably remember little of the discussions, but recall vividly the approach of Powers to a clinical problem. He first listens carefully to the history and the results of laboratory examinations. He always examines the patient carefully and his diagnosis and therapy always seem to come from what he sees and feels during this examination. He seeks the opinions of others in such a manner that the analysis of the case which is presented to him is not influenced by any opinion which he himself might have. The whole picture shows a wise and experienced man who is still learning medicine from the careful study of patients. The paths leading to wisdom in the care of infants and children are revealed to those who understand the spirit behind the example of Grover F. Powers.

THE LABORATORY AND THE COMMUNITY IN THE UNDERGRADUATE TRAINING OF A PHYSICIAN*

JOHN McK. MITCHELL**

Where is the knowledge we have lost in information. . . .
(T. S. Eliot)

The objectives of a medical education are not difficult to formulate. Stated without elaboration they are, first, to give the student a working knowledge of the basic scientific data upon which modern concepts of medicine are founded; and, second, to help him develop the ability to apply that knowledge to the prevention, diagnosis, and treatment of disease. It is additionally hoped that by the time the student leaves the guide-posts and shelters of the medical school he will not only be capable of applying scientific medicine at the bedside, but of planning and continuing his own further education.

The writer believes that many medical schools accomplish these objectives with a very fair degree of success and that the better students, when they graduate, possess a truly remarkable fund of information and the ability to apply it intelligently in diagnosis and treatment. On the other hand, instances illustrative of an almost unbelievable lack of appreciation of the rôle of emotions in the development and progression of disease, and of the influence of disease in the production of adverse emotional states, are all too easy to find: the man with cardiac decompensation who weeps at ward rounds suggests hyperthyroidism to the house staff; the woman with two abdominal surgical scars and a train of complaints is treated by a third abdominal scarification.

It is comparatively easy to find an explanation for such defects in understanding. One can also readily comprehend why the recent graduate fails to recognize the importance of familial and community relationships, of economic and social pressures in their effects upon the health of the patient. The great majority of students enter medical school directly from college, where they have been living apart from the everyday world. In medical school, for two years they spend their time in laboratory, library, and lecture room. Then, for several more years, their life is centered in the hospital. Here, to be sure, they are dealing with people but in large measure with sick people recently transplanted into a strange and awesome environment. Modern medical practice makes it inevitable that the care of these patients be conducted by a group of highly specialized physicians who all too often think of treatment in terms of the disease rather than of the

* From the School of Medicine, University of Pennsylvania, Philadelphia.
** Resident in Pediatrics, New Haven Hospital, 1926-1927.
Received for publication December 1, 1951.

person who is ill. Carried to its extreme, this can result in a cardiologist's thinking, for example, of man as a pumping station with a fascinating and complicated system of pipes and valves subject to manifold disturbances of power failure, pressure, blockage, and leaks. Nurtured first in an atmosphere of science for science's sake, weaned to a piecemeal diet of treatment by body systems, when the recent graduate begins to forage for himself in practice, need it surprise us if he fails to understand the importance of treating the person who is ill? Should we expect him to attach due importance to the rôle of emotions, to the fact that this patient has a family who care for him and for whose welfare he feels responsible? Should we find fault if in the beginning the young doctor may conduct himself in a manner that adds to the emotional disturbances of his patients?

Children enjoy merry-go-rounds, but adults soon weary of retreading the same circle. There would be no justification for the repetition of this preamble were there to be no tangential development. Every thoughtful medical educator recognizes the deficiencies cited, and there is a fair degree of agreement concerning the causes. Attempts at correction have been made, and the purpose of this article is to record two particular efforts now in action in the School of Medicine of the University of Pennsylvania.

A medical school curriculum bears to its graduates a relation similar to that of an architect's plan to the finished building. No matter how good the materials used or how well the separate parts may be built, they must be properly fitted into the right design. So, too, individual medical students and specific courses may be of the highest caliber, but they must be an integral part of a carefully planned curriculum if they are to result in a well-trained physician. At the same time, no curriculum can rise above the level of the actual teaching. If the courses to be described have attained any success, and we believe they have, total credit is due to the teachers responsible for their daily conduct and to the receptivity of the students with whom they have worked.

One man no longer builds a house; the end product is the result of the combined efforts of many men. It is more difficult today for the great individual teacher to stand out, for he, too, is more dependent upon the efforts of others than used to be true. This should not be taken to indicate that great teachers do not exist; by no means is this the case. Indeed, the volume of which this article is a part is being offered in acknowledgment and tribute to one of the greatest of modern teachers.

The Laboratory

*Experimental pathology in the training of a physician**

In the teaching of pathology to second year medical classes, the aim is to present the main principles of disease processes in a manner that

* This account of the course in experimental pathology is by Dr. Balduin Lucké, Professor and Chairman of the Department of Pathology in the School of Medicine of the University of Pennsylvania, quoted in entirety.

will make a foundation for the student's future clinical career. From the beginning the student is urged to realize that pathological disturbances are not static conditions but ever-changing processes that occur only in the tissues and organs of a living individual: in a particular patient or in a particular sick animal. The dynamics of disease are made evident to the student by considering from various aspects the developmental stages of disease processes, their progressions and their possible regressions, and the alterations of function that accompany alterations in structure. So far as possible the lesions in a given organ are related to disturbances in other organs and in the patient as a whole.

To accomplish these aims, the class, though listening as a unit to a series of lectures, is divided into eight groups, thereby permitting more individual teaching than is possible with a large undivided class. The several sections rotate through the various activities scheduled for the day: they work in the laboratories of pathologic histology, of gross morbid anatomy and of experimental pathology, have presented to them material from recent autopsies, participate in the performance of autopsies. In each of these activities the student is made aware that he is investigating lesions from an individual human being. In the laboratory of pathologic histology he is furnished with an account of the patient's clinical course, and he is asked to interpret the preparations he studies as to probable underlying mechanisms. In the laboratory of gross morbid anatomy, where he sees changes in organs that can be recognized with the unaided eye, a senior fellow from the Department of Roentgenology demonstrates and explains the relation of the Roentgen films to the lesions. At the presentation of fresh autopsy material or when participating in the performance of autopsies, the lesions are again related to the preceding clinical events. Thus the student is introduced to the practice of clinico-pathological correlation. At the same time he becomes cognizant of the principle that although most disease processes preserve a fairly definite pattern, their variability is far greater than that of normal processes.

In no part of his course is this fact more evident than in the laboratory of experimental pathology, and in no other of his activities does he see more intimately the pathogenesis of lesions. Some of his experiments are of relatively short duration, as when he studies alterations in capillary permeability or when he measures the directional movements of leukocytes under the influence of chemotropic stimuli. Most of his experiments, however, require several weeks or several months for completion, as, for example, the production of cirrhosis of the liver, the induction of tumors by chemical carcinogens, the development of cardiac hypertrophy on a renal basis, the changes following total body irradiation. In such experiments the student examines and cares for his animal much as later he will examine and care for his patient. He is studying at first hand pathologic processes in a living creature, and he is taught to handle his animals with consideration and gentleness.

Work in the laboratory of experimental pathology takes up about one-fourth of the time allotted to the course in pathology; it has helped the student to see pathology as a subject in which form and function are intimately interwoven, a subject dealing with processes that are forever changing in a living being, and with the changes, whether active or passive, that the body and its organs may undergo in disease.

The Community

A family health adviser service in the making of a physician†*

The purpose of this project is to provide an opportunity for a medical student to assume gradually increasing responsibility for the medical and related problems of a family assigned to the student on his admission to medical school and followed by him in the home, clinic, and hospital throughout the four years of his undergraduate training. Other teaching centers have given their third- and fourth-year students varying degrees of contact with families, but we are not aware of any program that, up to the present, provides such experience from the very beginning of medical training. At first it was necessary strictly to limit the number of students accepted for the project, but the number has been increased each year.

Suitable families known to the social service departmnt or to the hospital are selected and asked if they would like to have a "Family Health Adviser." There has been no difficulty on this score. The major responsibility, from this point on, is purposely left to the student, who describes the plan to his "family" and explains his own rôle as that of an adviser and coordinator only, since he is a "doctor in training." Although this is a hurdle of no mean height to many students, they are clearing it successfully. Indeed, some of the most gratifying aspects of the plan are the manner in which the students have handled difficult situations and the esteem they have won from their "families."

The frequency with which a student visits his "family" or sees its members in outpatient clinics or on hospital wards is left to him. Naturally, it depends on a variety of factors such as the occurrence of acute illness, the presence or absence of chronic ailments (diabetes, rheumatic fever, and the like), the birth of a child, or the development of problems of interfamilial relationship.

Faculty advisers (physicians and social service workers) are always available for personal consultation. This feature is looked upon as a necessity.

Each class group is divided into small sections that meet once a month with faculty advisers to discuss their families. This permits each student to gain intimate knowledge, from the members of his section, of other families. Meetings of the entire group for general discussion of selected subjects are also held once a month.

The program gives the student an opportunity to learn that individual problems or disease cannot be understood or treated apart from the social and economic stresses and strains of intrafamilial situations. He is obliged to develop a physician-patient relationship in which he assumes responsibility for the welfare of his family. Some criticism has been leveled at the program on the grounds that a first-year student is not ready for such responsibility. Our experience indicates that the very fact that he shares actual responsibility develops his caution and recognition of his own limitations. The success of the venture hinges largely on the student's having

---

* Since November 1951, this project has been supported by a grant from the Commonwealth Fund.

† A complete description of this course is to be found in an article entitled "The family in the training of medical students," by Hubbard, J. P., Mitchell, J. McK., Poole, M. L., and Rogers, A. M., Journal of Medical Education, 1952, *27*, 10-18.

ample opportunity to consult with faculty advisers. Physicians and social workers must be readily accessible to him, they must be skilled, and they must themselves possess an abiding interest in patients as people.

It is too soon to assess the end-effect of this program upon the eventual capacity of the graduate to handle more satisfactorily the manifold personal and emotional problems that beset his patients. It is not too soon, however, to say that these students already have a broader understanding of the origin and development of such problems. We are enthusiastic about it as it has developed to date, and our enthusiasm is shared by the participating students.

In years gone by, essentially every clinical teacher was a practitioner in the true sense of the word; he thought and practised in terms of home and family problems and carried this attitude into his daily teaching. The need for first-hand experience during student days was then not so great. While it is fashionable today for clinical instructors to pay lip service to the interplay of emotional, environmental, and physical factors, it is very difficult for the younger hospital staff member, himself the product of a system that paid scant attention to such annoying side issues, whose own experience is limited to the medical center network and who may be keeping one foot and half of his mind in the laboratory, to be so steeped in this interplay and its effect on the course of disease in the patient that he brings it into his daily teaching without conscious effort. This being true, we must counterbalance it by providing the student now with personal experience.

Here, then, have been presented two widely separated approaches to the problem of providing in the curriculum an opportunity for students to overcome certain defects accruing from the recent pattern of medical education. In one, a laboratory course in which he personally performs and follows animal experiments, the student observes and records and then makes deductions from what he has seen, done, and described. Thus, he parallels in the laboratory the process he will later utilize in bedside diagnosis. Having visualized disease as a process subject to alterations imposed by the interactions within a living being, he is closer to a realization of the importance of the reaction of the patient to the disease from which he is suffering.

The other course utilizes the community as a laboratory for an experiment in human relations in which the student is an active and responsible participant. It is time to forsake the once prevalent belief that nothing worthwhile in medicine is to be learned outside the hospital.

Our hope is that the graduate of tomorrow will approach clinical problems with a broader vision of their genesis and a firmer foundation upon which to base treatment, and that he will find some of the knowledge —that is to say, the wisdom—lost by his predecessors in the gathering of information.

CONGENITAL IDIOCY, SEXUAL INFANTILISM, AND DWARFISM

A Clinical Report of Two Cases with Autopsy in One Case*

CLIFFORD JOSEPH** and HERMAN YANNET†

Congenital hypopituitarism is a relatively rare condition, as is congenital idiocy. For this reason, their simultaneous presence in the same patient can hardly be attributed to chance. The occurrence of both of these clinical features in two patients stimulated this report. It is hoped that the publication of cases, exhibiting clinical combinations of this type, may eventually allow for a more adequate study of etiology and pathogenesis. The postmortem examination of one of these cases will also be presented.

Clinical Histories

Case 1. W.D.

This man was admitted to the Southbury Training School in 1948 at the age of 41 years. The family history showed no evidence of pertinent hereditary factors. The parents were of normal mental status, and physically not remarkable. There were nine pregnancies, including a miscarriage (fourth pregnancy). All the children are living and well except for one son who died in army service. Their intellectual status was within the normal range, all having gone through at least four years of high school. There was nothing in the history to suggest the presence of endocrine disturbances in any sibling or relative.

Past History. The patient was the result of the first pregnancy which was uneventful. Delivery took place at home, a physician attending, and was at term and spontaneous. The neonatal period was uneventful except for a short period of cyanosis at five days of age which was treated by mild stimulation and lasted for less than 30 minutes. There were no serious illnesses during infancy or childhood. Pertussis was diagnosed at seven years of age and was not unusual in its course. According to the parents, the mental retardation was recognized almost from birth and subsequent development was delayed in all spheres. He sat alone at three years, stood at six years, and walked with support at eight years, but never alone. He has never talked. He was always underdeveloped. Secondary sex characteristics never appeared. Although a reasonable layer of body fat developed, his extremities were always thin and rod-like. He was cared for at home until his admission to the school.

Physical examination. He was a poorly developed but moderately well-nourished man, of good color and in no discomfort. He was 110 cms. tall and weighed 34 kgs. The body fat distribution was suggestively feminine, being well marked around the

* From the Southbury Training School, Southbury, Connecticut, and the Department of Pediatrics, Yale University School of Medicine.
** Assistant Resident in Pediatrics, New Haven Hospital, 1949-1950.
† Assistant Resident in Pediatrics, New Haven Hospital, 1930-1931.
Received for publication December 1, 1951.

hips and mammary regions. The skin was of delicate texture, smooth and glistening, especially over the face and in areas where the skin was stretched. The cranial hair was coarse, of normal distribution, and without evidence of alopecia. There were fine creases of the face which, combined with the skin texture and complete absence of beard, gave the appearance of a prematurely old person. The head was 51 cms. in circumference and of normal configuration. The eyes, including the fundi, showed no abnormalities. The pupils reacted normally. The deep tendon and superficial reflexes were equal and active throughout. The ears, nose, and throat were negative. There was no abnormal glandular enlargement. The heart, lungs, and abdomen were within normal limits. Body hair was almost completely absent and there was no evidence of secondary sex characteristics. The genitalia were infantile in size—the penis measuring about 1.5 cms. in length, and the small, shrunken scrotum containing two undersized, soft testes. Muscle tone was generally diminished and there was evidence of minimal contractures at the hips and knees, which were functional in nature. The patient made inarticulate sounds in a rather high-pitched voice. The mental level was estimated at about one year. Roentgen ray study of the skeleton revealed the following: The skull was symmetrical with well-marked calcification in the choroid plexus. The sella turcica was small with no evidence of erosion. The bones of the upper and lower extremities appeared small and osteoporotic and there was failure of fusion of the epiphyses of the distal ends of the radii, ulnae, and metacarpals. The pelvis was asymmetrical with obliteration of the epiphyseal lines.

Laboratory studies. Blood serologic test for syphilis was negative. Peripheral blood showed no abnormalities. Routine urine examinations were negative. Twenty-four-hour excretion studies of urinary 17-ketosteroids on two occasions gave values of 2.7 mgms. and 3.0 mgms. respectively. On the same specimens a total creatinine of 570 mgms. and creatine of 198 mgms. were found. Serum electrolyte concentrations, including bicarbonate, chloride, sodium, potassium, phosphorous, and calcium were within normal ranges, as were the fasting blood sugar, cholesterol, protein, and nonprotein nitrogen levels. A serum iodine level of 7.4 micrograms per cent was obtained on one occasion. A sugar tolerance curve after the ingestion of 70 gms. of glucose was normal. The blood eosinophil drop four hours after the injection of 0.3 mgm. of adrenalin was approximately 40 per cent and probably within the normal range, indicating an adequate adrenocortical response to the adrenalin-stimulated pituitary adrenocorticotropic hormone.*

Comment. The history is essentially devoid of factors that might have any etiological significance except for the implication that both the endocrine disorder and the mental deficiency were probably prenatally determined. The positive findings, in addition to the idiocy, both on physical examination and by laboratory study, were as follows: (i) marked dwarfism; (ii) pronounced hypogonadism; (iii) reduced 17-ketosteroid excretion for age; (iv) no evidence of hypothyroidism; (v) no evidence of electrolyte disorder; (vi) no evidence of significant defect in carbohydrate metabolism. It would appear that a differential hypopituitary state existed affecting only those functions concerned with growth and gonadal development and function, while there was no evidence indicating significant involvement of the thyrotropic or adrenotropic hormones, except possibly in respect to androgenic functions.

---

* We are indebted to Dr. Paul L. Munson of the Department of Pharmacology of the Yale School of Medicine for the studies of the urinary 17-ketosteroids.

Case 2. J.C.

This boy was born in 1932 and admitted to the Training School in 1941 when almost nine years of age. The family history was noncontributory. The two younger siblings were alive and well and of normal intellectual status. No hereditary history of significance was obtained.

Past history. He was the result of the first pregnancy which was uneventful. Delivery at term was by breech extraction. Unfortunately, it was not possible to obtain adequate details concerning the delivery and the immediate postnatal period to evaluate the likelihood of cranial birth trauma. Bilateral club feet were noted at birth. Development was delayed in all spheres and mental retardation was detected from early life. He was cared for at home without too much difficulty until his admission to the School. There had been no serious illnesses.

Examination (1941). The head appeared large in proportion to the patient's body. The circumference was 53 cms., but the crown appeared high and the forehead prominent. Body configuration, which approximated a three-year-old child, was of normal proportions. The eyes including the fundi were negative. The heart, lungs, and abdomen were within normal limits. Muscular tonus and the reflex pattern were normal. Bilateral club feet were present, more severe on the left. The genitalia were infantile and the testes, small and soft.

Interval course. In June, 1942, he had his first convulsion, which was generalized. These became more frequent and were difficult to control in spite of apparently full anticonvulsive drug administration. They averaged two to ten per month. In July, 1945, he developed the first of a series of syncopal episodes which recurred once or twice per year until his death. These consisted of sudden shock-like states, during which he would become unconscious, cold and pale, and with markedly reduced blood pressure. At first, he was treated in the usual anti-shock manner with infusions, warmth, and head-lowered position, with recovery within 20-30 minutes. At various times, it was found that these spells were self-limited and would spontaneously clear in about the same time without specific treatment. It was felt that these episodes were probably due to abnormal mid-brain neuronal discharges. His general health was reasonably good except for one period of prolonged illness due to a lung abscess, probably related to aspiration, from which there was good recovery. He never developed signs of secondary sex characteristics. His physical examination, at the time the special laboratory studies were carried out, was as follows (1949 when eighteen years of age): There was marked dwarfism, the height being 125 cms. and weight 31 kgs., although the general proportions were not unusual. The head now measured 55 cms. with prominent forehead and suggestively elevated crown. The skin was soft, smooth, and without facial, axillary, or pubic hair. The penis was infantile, and the testes measured about 1 to 1.5 cms. in longest diameter. There were fine creases on the face over which the skin appeared drawn and glistening. The muscular tone appeared normal and the reflexes were physiological. There was no evidence of any specific neurological disorder. His mental level was estimated at twelve months. He made only occasional unintelligible high-pitched sounds. Roentgen ray studies revealed the following: The skull was globular in shape. There were no abnormal calcifications or digitations. The suture lines appeared within normal limits. The extremities, including the hips, showed, in addition to the small size, delayed fusion of hand and femoral epiphyses.

Laboratory studies. Blood serologic test for syphilis was negative. The peripheral blood, as in the preceding case, was normal. Many routine urine examinations were negative. Twenty-four-hour excretion studies of urinary 17-ketosteroids, on two occasions, were extremely low (less than 1.0 mgm.). On these specimens a total creatinine

of 374 mgms. and creatine of 157 mgms. were found. Serum electrolyte studies on many occasions, as well as cholesterol, NPN, and protein, were within normal limits. In two instances, however, associated with the shock-like episodes previously described, significant elevations of chloride and sodium were obtained (131 and 166 m. eq. per liter, respectively) which were considered as secondary to the accompanying dehydration since they returned to normal the day following adequate hydration. Blood iodine values were also normal (6.8 micrograms). The oral glucose tolerance curve was normal as were frequent fasting blood sugar levels.

Terminal course. He was in his usual state of health until May 1, 1950, when his grand mal spells greatly increased in frequency. He received our routine treatment of parenteral sodium phenobarbital to prevent status epilepticus. This was effective and his condition seemed good in the morning when he was prepared for breakfast. However, while being fed, he suddenly slumped over and rapidly expired. The autopsy was performed about seven hours' post-mortem.

Comment. It is unlikely that the breech delivery was the sole etiological factor related to the basic clinical picture this boy presented. The severe degree of mental deficiency in the absence of any demonstrable significant neurological defect, associated with other evidence of developmental defect (bilateral club feet and anomalies of the cerebral ventricular system seen at autopsy) strongly suggest a prenatally determined malformation. In this respect, as in the rather characteristic clinical picture and laboratory findings, this case strikingly resembled the first one. The immediate cause of death could not be determined even at autopsy examination. It was felt, however, that the boy died from vasomotor collapse probably due to an acute neuronal mid-brain discharge, similar in nature but more severe than those previously described.

*Autopsy report.** Only the pertinent findings are summarized.

Brain. The gross appearance, size, and weight were not remarkable. Microscopically, the sections of the cortex studied showed normal architecture. In the region of the lateral ventricles near the septum pellucidum, there was perivascular infiltration and gliosis, associated with many glial rests. The choroid tufts were atrophied. The cells of the fascia dentata were pale and a few blood vessels showed a mild perivascular infiltration, and one old hemorrhagic extravasate with yellow pigment and glial reaction was seen. Gliosis was evident throughout the white matter. Sections through the pons and pontine tegmentum showed what was interpreted as a congenital malformation of the ventricular system in the form of a ventricular diverticulum, including many small, closed cavities lined with ependyma. The capillary bed in the tegmentum was increased with obvious gliosis. There appeared to be significant cell loss in the reticular nucleus of the tegmentum pontis. In the region of the pyramidal decussation, one again noted the evident cell loss in the reticulata. Throughout the brain, many of the ganglion cells were pale and swollen, suggesting relatively recent neuronal changes which may be associated with anoxic states.

The changes in the central nervous system may be summarized as follows: (i) widely disseminated focal ganglion cell loss; (ii) gliosis; (iii) perivascular cellular infiltration; (iv) ventricular malformation.

---

* We are indebted to Dr. H. Bunting of the Department of Pathology and Dr. P. I. Yakovlev, formerly of the Department of Neurology and Psychiatry of the School of Medicine, for the study and evaluation of the post-mortem material.

Endocrine glands. Adrenals: These were smaller than normal with a combined weight of 10 gms. The cortex had an average amount of lipid. There was no discernible pigment within the zona reticulosa.

Testis: The combined weight was 18 gms. On section the gland was pinkish white. Many of the seminiferous tubules contained spermatids and immature sperm. No mature sperm were found. Interstitial cell groups were infrequent, composed of few cells and lacking the usual granular eosinophilic cytoplasm. There was no fibrosis or evidence of a previous inflammatory process.

Thyroid: The gland weighed 7 gms. The acini were of usual size and filled with deeply eosinophilic colloid and lined by cuboidal epithelium. No collections of lymphoid tissue and no fibrosis were seen.

Thymus: This was enlarged, weighing 45 gms., and showed an abundance of both medullary reticular and cortical lymphoid tissue. Hassall's corpuscles were numerous. No evidence of involution was present.

Pituitary: There was a striking deficiency of both acidophilic cells and basophilic cells in the anterior lobe. The posterior lobe appeared normal.

The changes in the endocrine glands may be summarized as follows: (i) deficiency of acidophiles and basophiles in the pituitary; (ii) absence of involution of the thymus; (iii) immaturity of the testes; (iv) reduced size of the adrenals.

Discussion

The combination of idiocy, dwarfism, and sexual infantilism presents a clinical picture that is readily apparent. As previously stated, the uncommon nature of each of these symptoms makes it unlikely that in both these patients they represent chance associations. For the same reason, it is unlikely that both these patients would represent similar atypical forms of the hereditary condition, first described in 1866, and now known as the Laurence-Moon-Biedl syndrome. The occurrence of pigmentary degeneration of the retina is almost universal in the latter condition. The mental defect is usually in the moron or borderline category; obesity and poly- or syndactylism are almost always present, while dwarfism is rarely striking.[3]

The widespread nature of the cerebral pathology in the form of focal ganglion cell loss and gliosis, the marked mental defect associated with partial pituitary dysfunction (dwarfism and sexual infantilism), and the apparent congenital nature of the condition would naturally suggest as the pathogenesis for the disorder a developmental abnormality of the central nervous system including the pituitary neural centers of the hypothalamic region. Speculation as to etiology would be futile at this time. Genetic factors (mutants or directly transmitted) must be considered as well as acquired prenatal conditions.

Some endocrine aspects of interest may be mentioned. In these children, as in the Laurence-Moon-Biedl syndrome, the evidence of dissociated pituitary dysfunction is intriguing. If secondary to developmental changes in the hypothalamic nuclei related to pituitary activity, the selective nature of the injurious agent to involve only certain of the multi-natured pituitary

glandular functions is difficult to understand. In neither of these patients was there evidence of significant interference with those functions related to electrolyte, carbohydrate, thyroid, or water metabolism.

The absence of thymic involution, as found in the post-mortem study of our second case, resembles the observation in castrate animals in whom involution of the thymus is delayed. In these laboratory animals, thymic involution may be accelerated by the administration of estrogens or androgens. In animals with intact gonads, the administration of pituitary gonadotropins will also accelerate thymic involution.[1]

The excretion of creatine was considered in the range to be expected of prepuberal children. The apparently small 24-hour total creatinine output (approximately 15 mgms. per kgm.) is presumably a reflection of the relative reduction of muscle tissue mass which was obvious clinically in both cases.

Summary

Two cases showing considerable clinical similarity including congenital idiocy, sexual infantilism, and dwarfism are described. The post-mortem examination of the brain of one of these patients showed widely disseminated focal ganglion cell loss, gliosis, and ventricular malformation. The changes observed in the endocrine glands were compatible with a primary pituitary deficiency.

The clinical picture is interpreted as the result of widespread cerebral maldevelopment, including the hypothalamic neural connections of the pituitary gland, and manifesting selective pituitary dysfunction involving primarily gonadotrophic and growth hormones, as well as severe mental defect.

References

1 Anderson, D. H.: The relationship between the thymus and reproduction. Physiol. Rev., 1932, *12*, 1.

2 Cockayne, E. A., Krestin, David, and Sarasby, Arnold: Obesity, hypogenitalism, mental retardation, polydactylism, and retinal pigmentation: The Laurance-Moon-Biedl Syndrome. Quart. J. M., 1935, *4*, 93.

3 Roche, M., Thorn, G. W., and Hills, A. G.: The levels of circulating eosinophils and their response to ACTH in surgery. N. England J. M., 1950, *242*, 307.

SELF-REGULATORY FEEDING IN A PREMATURE NURSERY*

FRANK H. HORTON,** LULA O. LUBCHENCO, AND HARRY H. GORDON†

With the assistance of
MISS DORIS M. GREENE, R.N., AND MRS. LOUVERTA BRUNKOW, R.N.

Self-demand or self-regulatory feeding has been described for full-term infants from birth,[5, 10, 15] and for prematurely born infants after discharge from the hospital.[2] It had been our custom at the Colorado General Hospital to employ self-regulatory feedings for many premature infants during the last few days of their hospital stay, if the nurses' and doctors' contacts with the mothers indicated the feasibility of this regime upon discharge of the infant. It was hoped that this might decrease some of the behavioural problems apt to arise in premature infants subject to the highly restrictive routines of the nursery.[3, 9, 14] Because adequate, interested nursing service was available, self-regulation of feedings was then extended to younger infants in the premature nursery.

The present report is concerned with some of the results of this attempt. Two types of data are presented. One is an analysis of the records of twenty infants who did well. The second consists of case reports of five infants for whom the method was not successful. No attempt has been made to determine the relative incidence of successes and failures for reasons which will be discussed below.

SUBJECTS AND METHODS

Analysis of feeding charts

Records have been analyzed for twenty healthy infants (six male and fourteen female) born prematurely in the Colorado General Hospital or transferred to its Premature Infant Center‡ because of inadequate facilities for proper care at the place of birth. Birth weights ranged from 1.30 to 2.27 kg. The mean weight at the beginning of observations was 1.90 kg. (range 1.55 to 2.21) and the mean age at the beginning of observations was seventeen days (range two to forty-five days). Only infants for whom at least eight days of study were available for analysis are included. The mean number of days of observation was fourteen (range eight to twenty-five).

* From the Department of Pediatrics, University of Colorado School of Medicine, and the Colorado General Hospital, Denver, Colorado.
** Assistant Resident in Pediatrics, New Haven Hospital, 1949-1950.
† Assistant Resident in Pediatrics, New Haven Hospital, 1931-1932.
‡ The Premature Infant Center was established at the Colorado General Hospital in 1947 by the Colorado State Health Department with funds supplied by the U. S. Children's Bureau, Federal Security Agency.
Received for publication December 1, 1951.

Infants were chosen for trial on a self-regulatory feeding regime on the basis of the nurses' reports that they were vigorous, sucked well, and were able to cry, and to maintain good color and stable body temperature without oxygen therapy or external sources of heat. The signs of hunger recognized by the nurses are described as the following:

(i) Sucking on the fists.

(ii) Excessive movement, especially wriggling motions whereby the infant propelled himself to the head end of the bassinet.

(iii) Crying, the character of which varied from infant to infant when it signified hunger.

When an infant exhibited these signs of hunger, he was picked up and fed in the nurse's arms with frequent periods of "burping" during the feeding. In the experience of these nurses few infants exhibited signs, due to soiled or wet diapers, which might be confused with hunger.

All persons directly concerned with the feeding of the infants were either nurses with long experience in the care of premature infants or graduate and undergraduate student nurses and nurses' aides under the close supervision of instructing supervisors. A definite attempt was made to employ as staff nurses only those who had a sincere interest in the handling of young infants. The duties of the nursing personnel were solely in the nurseries. Medical care was given by pediatric residents under the supervision of two members of the pediatric attending staff.

The feeding mixture used in this study is high in protein and low in fat, essentially that described by Powers.[11,12] As prepared for this study, it consisted of 18 grams of powdered, partially skimmed cows' milk (Alacta) and 12 grams of Dextrimaltose with water added to make 150 cc.; it supplied approximately 0.8 Calories per cc. The feeding mixtures were prepared with terminal sterilization in a central formula kitchen adjacent to the nursery. In addition, each infant received daily a water-soluble polyvitamin dispersion.

Results

The results are presented in Tables 1 and 2 and Figure 1. The mean daily weight gains ranged from 12.0 to 18.3 grams per kg. with the exception of one infant (C-16), who was permitted self-regulation at the age of two days and whose mean daily weight gain was 9.0 grams per kg. The average of the mean weight gains was 14.2 grams per kg. per day, corresponding to an average total daily gain of 30 grams. Such weight gains may be considered satisfactory by comparison with rates of gain in utero during the last months of pregnancy,[13,17] and by customary standards of extrauterine weight gain.

The average of the mean daily caloric intakes of the infants permitted to choose the amounts of their feedings averaged 119 Calories per kg., virtually the same as that determined in a metabolic study.[5] The wide range of the

TABLE 1

DAILY WEIGHT GAIN AND CALORIC INTAKE OF PREMATURE INFANTS ON SELF-REGULATION

*Subject**	*Birth weight*	*Weight at start of observation*	*Age at start of observation*	*Duration of observation*	*Mean weight*	*Mean daily weight gain*	*Daily intake—Calories per kilogram†*				
							Minimum	*Maximum*	*Mean*	*S.D.‡*	*Coefficient of variation*
	Kg.	*Kg.*	*Days*	*Days*	*Kg.*	*Gm./Kg.*					*%*
C-1	1.59	2.01	19	8	2.14	15.0	116	155	135	9	6.6
C-2	1.94	1.90	12	15	2.44	12.3	73	144	115	18	15.6
F-3	2.27	1.81	12	16	2.08	16.1	72	152	107	26	24.3
G-4	1.73	1.84	21	11	2.00	13.5	113	187	150	19	12.6
S-5	1.95	1.57	8	10	1.69	14.0	51	110	85	25	29.3
H-6**	1.81	2.20	28	15	2.45	14.0	96	168	132	22	16.6
W-7	1.94	2.05	15	14	2.35	18.3	84	197	144	32	22.2
O-8	1.54	1.55	16	9	1.67	15.0	74	140	104	25	24.0
C-9	2.12	1.98	14	11	2.14	13.0	77	126	106	13	12.2
C-10	2.00	2.21	13	9	2.41	18.2	90	136	115	17	14.7
K-11	2.14	1.97	7	16	2.21	13.4	70	139	94	22	23.6
W-12	1.68	1.63	4	25	1.97	13.7	60	144	101	19	18.8
I-13	2.25	2.07	9	9	2.21	14.2	70	112	94	10	10.6
G-14	1.72	1.64	6	21	1.94	14.7	68	129	100	11	11.0
T-15	1.70	1.84	20	14	2.05	14.7	104	160	140	18	12.8
C-16	2.16	1.98	2	13	2.00	9.0	87	147	125	19	15.6
J-17	1.45	1.91	32	12	2.10	12.0	96	176	139	21	15.1
H-18**	1.70	1.95	20	14	2.20	16.0	101	169	128	14	10.9
M-19	1.30	2.12	45	15	2.33	12.4	91	149	121	21	17.3
S-20	1.45	1.84	31	16	2.07	14.5	127	184	149	17	11.4
MEANS	1.83	1.90	17	14	2.12	14.2	86	151	119	19	

* Infants C-1 through H-6 were males.

** Twins.

† Feeding mixture consisted of powdered ½-skimmed milk (Alacta), 18 grams, Dextrimaltose #2, 12 grams, diluted with water to 150 cc. (1 cc. = .8 Calorie).

‡ Standard deviation.

means, from 85 to 150 Calories per kg. per day, and of the coefficients of variability—from 7 to 29%, stresses the need for individualization in feeding infants.[4]

In Table 2, data are presented on the frequency of feedings, the length of the intervals between feedings, and the maximum variation for each infant

TABLE 2

INTERVALS OF FEEDING AND VOLUMES OF INTAKE OF PREMATURE INFANTS ON SELF-REGULATION

	Number of feedings per day			*Intervals between feedings*		*Amount of individual feedings on day of maximum variation in amount*			
*Subject**	*Minimum*	*Maximum*	*Mean*	*Range of minima*	*Range of maxima*	*Age*	*Minimum feeding*	*Maximum feeding*	*Difference*
				Hours	*Hours*	*Days*	*cc.*	*cc.*	*cc.*
C-1	5	7	6	2 -3½	4½-7	34	105	150	45
C-2	4	6	5	2½-4½	4½-7	17	30	60	30
F-3	3	6	5	3 -5½	5 -15	28	30	90	60
G-4	5	7	6	½-4½	4 -9	36	60	105	45
S-5	4	5	4	2½-5	6 -11½	24	40	60	20
H-6**	4	6	5	3 -5	4 -8½	33	50	90	40
W-7	3	7	5	1½-4	4 -9	20	50	120	70
O-8	3	6	5	2 -5	5 -13	24	30	60	30
C-9	4	7	5	1 -5	5 -7	16	30	60	30
C-10	4	6	5	2 -4½	4½-8½	21	60	90	30
K-11	4	6	6	1 -4½	5 -9	17	15	60	45
W-12	3	5	5	2½-6	6 -12	17	30	70	40
I-13	4	7	6	1 -5	4 -7½	21	55	90	35
G-14	4	5	5	1 -5½	5½-14	28	30	90	60
T-15	4	6	5	2½-4½	5 -10	23	40	90	50
C-16	4	6	5	2½-5	5 -7½	10	30	75	45
J-17	4	6	6	1½-4	5 -8	41	30	90	60
H-18**	5	6	6	2 -4	4½-8	23	30	60	30
M-19	4	6	5	2 -5	5 -10	61	90	120	30
S-20	4	7	5	2 -5	4½-8	36	30	75	45

* Infants C-1 through H-6 were males.
** Twins.

in the amount of individual feedings on a single day. The minimum number of feedings per day for the individual infants was three, four, or five; the maximum number was five, six, or seven. The mean number of feedings for the individual infants was, with the exception of Infant S-5, five or six, a uniformity which may have been partially dependent on consistent judgments as to hunger by a relatively constant nursing staff.

The ranges of the minimum and maximum intervals found for each infant show considerable variation; for example, Infant G-4 showed minimum

intervals (on different days) varying from one-half to four and one-half hours. Infant F-3 showed maximum intervals varying from five to fifteen hours. The maximum variations in the amount of individual feedings in any one day for each infant ranged from 20 to 70 cc. and averaged 40 cc. Infants frequently took as little as 30 cc. at one feeding and as much as 60, 75, or 90 cc. at other feedings on the same day.

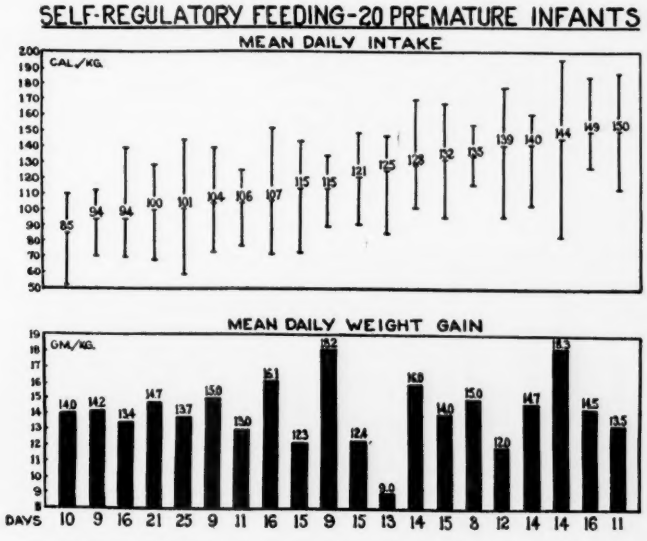


FIG. 1. The vertical lines in upper part of chart indicate the variations in daily caloric intake. The bars indicate maximum, mean, and minimum intakes for each infant. The observations are arranged from left to right according to ascending mean caloric intakes. The columns in the lower part of the chart are the mean daily weight gains in grams/kg.

CASE REPORTS

Five case reports are presented to illustrate some of the causes of failure of self-regulation. No attempt has been made to determine the proportion of infants admitted to the nursery for whom this method of feeding proved feasible.

Case 1. Failure due to inadequate nursing care at the time of trial.

B.B., white male, CGH #37812, was born September 2, 1951, weighing 2.12 kg., and because of his vigor was admitted to the full-term nursery. Since he was to be relinquished to an agency for adoption, he was fed artificially. The usual progression from 5% glucose in water to an evaporated milk-Karo mixture, finally containing 0.75 Calories per cc., was followed. Self-regulatory feeding was attempted beginning on the second day of life. He took six feedings of 30-45 cc. per day but lost weight steadily. On September 9, the seventh day of life, a one-half skimmed milk-mixture was substituted, because occasionally a large, premature infant may have difficulty in absorbing

fat.[7] The infant continued, however, to lose weight for five more days, and on September 18, age sixteen days, he was taken off demand regime because of failure to gain adequately.

During this time the full-term nursery was crowded and several staff nurses were absent. The reports were that the baby did cry when hungry but by the time a nurse could find time to feed him, he would be asleep and since he was on self-regulation he was not awakened for feeding. It was estimated that he awoke about every three hours. He developed sore buttocks in the absence of loose stools, and slight excoriation of knees and face, indicating inadequate nursing care. Repeated physical and laboratory examinations failed to reveal evidence of illness. He was sent home weighing 2.19 kg. on September 20, the eighteenth day of life, on recommendation of the resident, who noted: "Believe this baby will do better at home where he can have more TLC (tender loving care)." The adoptive mother returned with him to clinic after four days with the report: "Oh, he was hungry. He ate every three hours during the day and about every two hours at night." The actual number of feedings did not, however, exceed eight to nine per 24 hours. The interval increased to three to four hours after one week. He gained 250 grams during the first four days at home.

Case 2. Failure because of inadequate hunger in an infant weighing 1.40 kg. at time of first trial, with success later when infant weighed 1.80 kg.

G.K.N., white female, CGH #35433, was born June 11, 1951, weighing .90 kg. She was admitted to the Premature Center the day after birth and progress was satisfactory for the first ten days. On June 21 she was listless and there was blood on the gavage tube. A blood culture showed staphylococcus aureus. She responded well to antimicrobial therapy, and on July 26, at forty-five days of age, weighed 1.38 kg. At this time she was taking 34 cc. of formula every four hours by nipple, and the nurses reported: "Ate well, hungry a.c. and p.c., very active." On July 27, weight 1.41 kg., self-regulatory feedings were begun. On July 28 she took five bottles of 45 cc., totalling 155 cc. per kg. for the day. During the next two days she received 150 cc. and 190 cc. per kg. and then the resident noted that she stopped demanding. The nurses also commented that she "ate slowly, sleeping all evening. No cry heard." On July 31 and August 1, she ate only three times in 24 hours, and received 115 and 105 cc. per kg. She lost 50 grams in weight in these two days, although there were no other signs of illness. On August 2, scheduled feedings were resumed every four hours with a prompt gain in weight and activity.

One week later, August 10, when she weighed 1.80 kg., the nurses noted, "Hungry a.c. Ate very eagerly, would have taken more." After self-regulatory feedings were begun again the notes read: "Ate well, satisfied." She maintained an intake of about 150 cc. per kg. per day for the next ten days, and increased this to approximately 200 cc. per kg. per day before discharge at 99 days, weight 2.55 kg.

Case 3. Failure because of loose stools which occurred after increase in intake.

J.M.D., white female, CGH #32507, was born March 7, 1951, weighing 1.50 kg. She did well on the usual premature regimen, and by March 25 she was taking 120 cc. per kg. per day in eight gavage feedings at three-hour intervals. On March 28 the nurses noted: "Gavaged well. Hungry a.c." By April 2 she was taking all eight feedings by nipple in quantities which totalled 140 cc. per kg. per day. On April 3, age 27 days, weight 1.73 kg., she was permitted self-regulatory feedings. The quantity of individual feedings increased from 30 cc. to 50 cc. for the remainder of the day. On April 4, she requested five feedings of 45 to 60 cc. (135 cc. per kg.); April 5, 165 cc. per kg.; and on April 6, four feedings totalling 150 cc. per kg. On April 7, she received 175 cc. per kg. (140 Calories per kg.) and developed loose stools. These cleared on boiled

skimmed milk given on demand during the next two days, even though she received 220 cc. per kg. (90 Calories per kg.). She was tried again April 10 on the one-half skimmed milk-carbohydrate mixture. She took 190 cc. (150 Calories) per kg. and loose and watery stools again resulted. Without change of feeding mixture, she was given 150 cc. per kg. on a four-hour schedule April 11, with prompt resumption of soft formed stools in the next 24 hours.

Case 4. Partial failure because infrequent, large feedings led to regurgitation.

E. G., white female, CGH #36298, was born July 13, 1951, weighing 1.35 kg., and was admitted with her twin to the Premature Center on the day after birth. On July 20, the nurses noted some difficulty with feeding. "Frequent coughing with feeding. Ate well. Hungry. Regurgitated 2 cc. formula with mucous." Subsequent feedings on that day were taken well, and it was noted: "Hungry a.c. Ate well." By July 23, she had regained her birthweight, and was taking 155 cc. per kg. per day. The resident noted: "Seems vigorous and takes nipple well."

On July 26, because she was hungry and cried so much, self-regulatory feedings were started, even though coughing occurred with feedings. The nurses noted: "Ate well, but seems to choke easily." On July 27, she took 190 cc. per kg. Two of the five feedings were taken well, but it was noted for the others: "Coughed with emesis of large amount of curdled milk." On July 30, she received 230 cc. per kg. Choking and coughing occurred with every feeding. Regurgitation was noted frequently after August 3. Repeated physical examinations and laboratory studies which included fluoroscopy with a barium swallow failed to reveal any abnormality. On August 15, the fluid intake per feeding was restricted to 60 cc., a total of 180 cc. per kg. per day, and from August 16 until discharge, on August 25, there was only one note of coughing or gagging with feeding, and only twice was regurgitation recorded. Her total intake was high, approximately 200 cc. per kg. per day, because there were six to seven feedings in 24 hours (instead of the four to five on unrestricted quantities).

The resident noted just before discharge: "Ready to go home after mother has fed her one or two times. May have to be discharged on restricted amount and flexible time schedule."

Case 5. Failure in an infant with congenital heart disease because of cardiac decompensation precipitated by increased intake.

D.J.S., white male, CGH #12428, was born July 11, 1949, weighing 1.62 kg., and was transferred to the Premature Center on July 25 with his twin. At birth a harsh systolic murmur had been heard. On August 9 a diagnosis of coarctation of the aorta and possibly an additional cardiac defect was made. He became increasingly cyanotic after feedings, necessitating oxygen, but there was no enlargement of the liver, nor were râles heard in the chest. Because of nurses' notes such as: "Took nipple well. Acts hungry p.c. Awake and fussing," it was felt that he might be more contented, with resultantly less cyanosis, if feedings were given on self-demand. These were begun on August 16. The volume per feeding increased from 45 to 75 cc. and he seemed satisfied during the next few days. On August 23, his intake was 220 cc. per kg. He gained 200 grams the next day, and the nurses reported: "Ate well, respiration rapid, hands and feet seem edematous." Edema, tachypnea, and tachycardia led to the diagnosis of heart failure. On August 25 his intake was restricted, mercuhydrin was given and "copious voiding resulted, with loss of 150 grams in weight and marked decrease of the pitting edema." He was placed on a feeding mixture of which the base was partially low NaCl milk (Lonalac), and no further unusual weight gain or edema was recorded. He was not tried on demand feedings again, but because he cried a great deal, solid foods were added, and flexibility in the prescribed feedings gave him inter-

vals of 3 to 4½ hours between feedings. He was discharged October 2, 1949 weighing 3.88 kg. at 83 days of age.

Comment

What are the conditions which make feasible the use of self-regulatory feeding regimen for premature infants in the nursery? These will be discussed under three headings: (a) the feeding mixture, (b) the infant's vigor and the nursing service, and (c) the medical supervision. The attitude of the mother is not a factor in the highly artificial surroundings of the usual premature nursery, but is, of course, a crucial consideration on discharge of the infant.

If a self-regulatory schedule is to be tried, then the feeding mixture must be one which is qualitatively adapted to the premature infant's needs and which will consistently produce a satisfactory weight gain. A low fat, high protein mixture meets these specifications[6, 12] and is recommended for the infant who, because of small size, will be placed in a nursery under isolation precautions which will prevent his being suckled by his mother.

With such a feeding mixture, one may attempt to determine whether the infant's appetite will serve as a satisfactory guide to the quantities necessary to produce adequate weight gain as well as contentment. This attempt presupposes that the infant be vigorous and able to make his hunger apparent, and that the nurses be qualified by long experience and interest in newborn infants as individuals. In the present study, relatively consistent nursing judgment both in choice of infants for the study and in interpretation of the signs of hunger were probably partially responsible for the relative constancy in the number of feedings (Table 2). It did not, however, prevent failures such as those described in Cases 1, 2, and 4.

The nurses reported no increase in their work when feeding infants on a self-regulatory regime. On the evening and night shifts, when the ratio of personnel to infants was low, the nurses reported less tension than from attempts to meet an arbitrary schedule which was never kept because of the impossibility of feeding all the infants at the time designated in the doctor's orders. In a premature nursery service usually close to its capacity of twenty beds, the nurses reported comfortable efficiency when approximately half the babies were on a fixed schedule and half on self-regulation.

The proportion of infants for whom self-regulatory feedings proved effective depended particularly on the pediatric resident rotating through the nursery service every two months. Since the whole procedure is considered experimental and since its purpose is to teach respect for individuality of the infants, it was not deemed proper to foist the views of the authors on the residents. This would have smacked of what has been termed, "rigidness about being flexible."[1] Some residents were quite content to allow a premature infant to be fed as much or as little, and as often as demanded, so long as the infant's physical condition and weight gain were satisfactory. An occasional resident, either because of previous pediatric training or his

own anxieties, was hesitant to permit self-regulation by the infant. It usually took a resident from two to four weeks to learn to trust the nurses' judgment about the feasibility of trying self-regulatory feedings. The situation was frequently complicated by the fact that he was simultaneously ordering the feeding schedules for several small infants, too weak to suck or swallow, and for them the emphasis was on not exceeding their ability to retain the amounts gavaged. With increasing experience and faith in the nurses, came a willingness to relax the schedules for the more vigorous babies, and this sometimes led to premature enthusiasm, soon corrected by a failure or two.

Data are not available as to the attitudes of the mothers of the twenty infants for whom hospital records are herein reported, because all but three were followed by private physicians after discharge from the hospital. In general, it has been found that most parents seemed relieved to learn that their premature babies could be fed on a self-regulatory regime at home. Many mothers stated in the clinic that they had fed previous infants this way regardless of what their physicians instructed them. Another mother reported feeding her infant for 15 to 30 minutes every one or two hours. It is in this background that "chronic resistance to sleep" may easily develop.[18] On the other hand, one mother who said she fed her infant when he was hungry further stated, "I work it so that I feed him about 10:00 or 11:00 P.M., before we go to bed, so that I can get some sleep." Such a procedure, based on mutual respect for individuality, seems a reasonable practice.

Summary

1. Twenty prematurely born infants, vigorous enough to express signs of hunger, were permitted to regulate the amounts and intervals of their feeding under careful nursing and medical supervision. The feeding mixture used consisted of powdered, partially skimmed cows' milk fortified with Dextrimaltose and diluted with water to give a low fat, high protein mixture containing 0.8 Calories per cc. The mean daily caloric intakes for periods of from 8 to 25 days ranged from 85 to 150 Calories per kg. of body weight and averaged 119. The mean daily weight gains, with one exception, ranged from 12.0 to 18.3 grams per kg. and averaged 14.2. The corresponding average total daily gain was 30.0 grams. The mean number of feedings per day was with one exception five to six. The minimum number of feedings per day for the individual infants was three, four, or five; the maximum number was five, six, or seven. Minimum intervals between feedings ranged from ½ to 4½ hours; maximum intervals ranged from 5 to 15 hours. The maximum differences in amounts of individual feedings in any one day ranged from 20 to 70 cc. and averaged 40 cc. Use of self-regulatory feeding permitted introduction of the concept of respect for individuality, both of infants and of personnel, into the nursery for premature infants.

2. Five case reports illustrating some causes for failure of self-regulatory feeding were presented. These included inadequate intake because of nursing shortage or too early trial, and excessive intake which led to regurgitation or loose stools.

Conclusions

With qualified, interested nursing service, careful medical supervision, and a proper feeding mixture, self-regulatory feeding may be tried for vigorous premature infants. If successful, satisfactory weight gains will result and psychological benefit should accrue for those infants deprived of an opportunity to suckle from their mothers. Experience with large numbers of infants in an adequately staffed nursery is necessary to permit trial of the method.

References

1 Coleman, J.: Personal communication.

2 Glaser, K.: Semi-self-demand feeding schedule for prematurely born infants. Am. J. Dis. Child., 1948, *75*, 309.

3 Gordon, H. H.: The feeding of premature infants. Am. J. Dis. Child., 1947, *73*, 713.

4 Gordon, H. H. and Levine, S. Z.: The metabolic basis for the individualized feeding of infants, premature and full term. J. Pediat., S. Louis, 1944, *25*, 464.

5 Gordon, H. H., Levine, S. Z., Deamer, W. C., and McNamara, H.: Respiratory metabolism in infancy and childhood: XXIII, Daily energy requirements of premature infants. Am. J. Dis. Child., 1940, *59*, 1185.

6 Gordon, H. H., Levine, S. Z., and McNamara, H.: The feeding of premature infants, a comparison of human and cow's milk. Am. J. Dis. Child., 1947, *73*, 442.

7 Gordon, H. H. and McNamara, H.: Fat excretion of premature infants: I. Effect on fecal fat of decreasing fat intake. Am. J. Dis. Child., 1941, *62*, 328.

8 Jackson, E. B., Olmsted, R. W., Foord, A., Thoms, H., and Hyder, K.: A hospital rooming-in unit for four newborn infants and their mothers. Pediatrics, 1948, *1*, 28.

9 Koenig, H.: The care of premature infants. Child, Wash., 1940, *5*, 65.

10 Montgomery, J. C.: Self-demand feeding for the newborn. Harper Hosp. Bull., Detr., 1946, *4*, 205.

11 Powers, G. F.: Comparison and interpretation on a caloric basis of the milk mixtures used in infant feeding. Am. J. Dis. Child., 1925, *30*, 453.

12 Powers, G. F.: Some observations on the feeding of premature infants based on twenty years experience at the New Haven Hospital. Pediatrics, 1948, *1*, 145.

13 Scammon, R. E. and Calkins, L. A.: *Development and growth of the external dimensions of the human body in the fetal period.* Minneapolis, University of Minnesota Press, 1929.

14 Shirley, M.: A behaviour syndrome characterizing prematurely-born children. Child Develop., 1939, *10*, 115.

15 Simsarian, F. P. and McLendon, P. A.: Feeding behaviour of an infant during the first twelve weeks of life on a self-demand schedule. J. Pediat., S. Louis, 1942, *20*, 93.

16 Spock, B.: Chronic resistance to sleep in infancy. Pediatrics, 1949, *4*, 89.

17 Streeter, G. L.: Weight, sitting height, head size, foot length and menstrual age of the human embryo. Publication 274, Carnegie Institution of Washington, 1920. Contr. Embryol., Carnegie Inst., 1920, *2*, 143.

VITAMIN D AND CITRATE METABOLISM: STUDIES ON RACHITIC INFANTS*

HAROLD E. HARRISON** AND HELEN C. HARRISON

There are many reasons for considering the possibility that the metabolism of citrate is interrelated with the physiological effects of vitamin D and with the equilibrium of calcium and phosphorus in the body. Hamilton and Dewar[10] and Shohl[17] demonstrated that the addition of citrate to rachitogenic diets resulted in prevention or cure of rickets in rats. Subsequently, Shohl and Butler[19] showed that the feeding of mixtures of sodium citrate and citric acid to rachitic infants on a milk diet produced healing of the rickets although no vitamin D was given. Since the administration of dicarboxylic acids which do not form complex ions with calcium does not cause healing of rickets,[17] it is possible that the effect of oral citrate is related to its property of reducing the concentration of ionized calcium by virtue of the formation of an undissociated calcium citrate complex.[11] Dickens[5] added further interest to the possible rôle of citrate in bone formation by his studies of the citrate content of bone. He noted that bone contained appreciable amounts of citrate which was bound to the bone salt so that it was not eluted by water. The citrate content of the bone of a rachitic animal was found to be less than that of normal bone. Nicolaysen[18] extended this particular phase of the study and found that the bone citrate of rachitic rats was reduced to a greater extent than was the calcium so that the molar ratio of citrate to calcium in rachitic bone was less than that found in the bone of normal rats. The presence of citrate in bone could be merely another consequence of its reaction with calcium to form an undissociated complex and may not necessarily indicate any participation of citrate in the primary reactions leading to deposition of bone salt. The possibility that the metabolism of citrate might be altered in the vitamin D deficient subject developed from a study by Freudenberg,[8] which was concerned with the effect of vitamin D on the urinary excretion of organic acids in rachitic infants. Freudenberg suggested that the total organic acid excretion was high in the rachitic infant and was reduced by vitamin D therapy but his results were inconclusive. He had also determined separately the citrate content of the urine, and although there was considerable variation from day to day there did seem to be a real increase of citrate excretion following vitamin

* From the Department of Pediatrics, the Johns Hopkins University School of Medicine, The Harriet Lane Home of the Johns Hopkins Hospital, and the Pediatric Division of the Baltimore City Hospitals. Aided by grants from the American Pediatric Society, the Nutritional Foundation, and the Playtex Park Research Institute. Presented before the Society for Pediatric Research, May, 1951.

** Resident in Pediatrics, New Haven Hospital, 1934-1935.

Received for publication December 1, 1951.

D therapy. This prompted us to study the concentration of citrate in the serum and the excretion of citrate in the urine of rachitic infants before and after treatment with vitamin D.

Methods

The subjects were ten infants who had the characteristic clinical, x-ray, and biochemical evidences of active rickets and who had received little or no vitamin D prior to admission to the hospital. These infants were placed on a uniform diet consisting chiefly of whole cow's milk plus ascorbic acid and, for the older infants, supplements of cereal and vegetables. Repeated determinations of serum calcium, phosphorus, alkaline phosphatase, and citrate were made before and after treatment with vitamin D. The chemical methods used were as follows: calcium, Kramer and Tisdall[13];

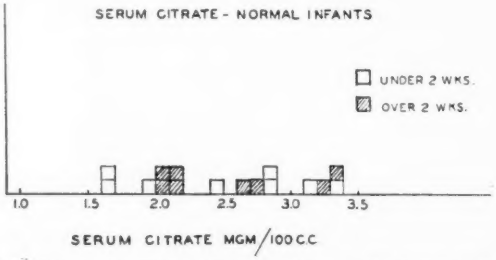


Fig. 1. Distribution of the values for serum citrate in the serum of normal infants. Determinations in infants under two weeks of age designated by open squares, those in infants between two weeks and two years of age by squares with diagonal lines.

phosphorus, Fiske and Subbarow[8]; alkaline phosphatase, Bodansky[3]; and citrate, Natelson, Pincus, and Lugovoy.[14] All blood samples were obtained in the fasting state to avoid changes of serum citrate due to carbohydrate ingestion.[15] In the infants on a four-hour feeding schedule the sample was obtained immediately before a feeding. After a preliminary period of observation, vitamin D_2 was given in a single dose of 600,000 units injected intramuscularly. This route was used in an effort to obtain uniformity of dosage. Serial x-ray examinations of the bones were made to correlate the anatomical evidences of healing with the changes in the serum levels of calcium, phosphorus, and citrate. In three infants the urine was collected quantitatively and the daily excretion of citrate determined before and after vitamin D therapy. The urine was collected in bottles containing 15 to 25 cc. of 10% acetic acid to prevent bacterial destruction of citrate.

Results

The distribution of the values for serum citrate in a group of normal infants under two years of age is shown in Figure 1. The average value for the entire group of 16 infants is 2.5 mg. per 100 cc. with a standard deviation of $\pm$ 0.59. The variability seems to be somewhat greater in the newborn infants than in the older group. The average value found in the entire group is in good agreement with the average concentration of 2.8 mg. per 100 cc. found in a group of normal children by Natelson, *et al.*,[15] and the

average value of 2.4 mg. per 100 cc. reported by Hagelstam[9] in normal subjects.

Table 1 summarizes the observations in a four-month-old rachitic infant. Prior to therapy the concentrations of serum citrate were found to be 1.5 and 1.6 mg. per 100 cc. Following injection of 600,000 units of vitamin D there was a prompt rise of the serum citrate level which increased progressively to a maximum of 3.6 mg. per 100 cc. approximately two weeks after

TABLE 1

EFFECT OF VITAMIN D UPON THE CONCENTRATIONS OF SERUM CITRATE AND URINARY EXCRETION OF CITRATE IN AN INFANT WITH RICKETS

A.C. AGE 4 MOS.

Day	P	*Serum* Ca *Mg./100 cc.*	*Cit.*	*Urine Cit. Mg./day*
1	3.8	9.1	1.5	
6				67
7	3.8	10.3	1.6	83
8				86
9		*Vit. D, 600,000 units*		
10				100
11				92
12				109
13				103
14	5.2	10.9	2.9	
17				133
18				143
19				126
20	6.4	10.3	3.2	146
21				160
22				162
25	7.3	12.0	3.6	
40	6.7	11.4	3.0	
376	6.2	10.5	2.4	

therapy. The increase in concentration of serum citrate paralleled the rise of the values for serum phosphorus and coincided with healing of the bone lesions as shown by x-ray examinations. A definite elevation of the concentration of serum calcium also occurred, but this appeared to lag behind the increase of the levels of serum citrate. The urinary excretion of citrate rose immediately following the injection of vitamin D, increasing from an average pre-treatment level of 70 mg. per day to a maximum value of 162 mg. per day following vitamin D.

A similar course of events in another infant with rickets (A. S., age 18 months) is shown in Table 2. The serum citrate levels which were 1.9 and

1.8 mg. per 100 cc. before therapy increased to a high value of 3.8 mg. per 100 cc. following the injection of 600,000 units of vitamin D. The urinary excretion of citrate increased from an average pre-treatment level of 83 mg. per day to a maximum value of 155 mg. per day. The rise of the values for serum and urine citrate coincided again with other evidences of vitamin D effect, viz., increase of the concentration of serum phosphorus and, to a lesser extent, of the concentration of serum calcium, in addition to evidences of healing by x-ray.

TABLE 2

EFFECT OF VITAMIN D UPON THE CONCENTRATIONS OF SERUM CITRATE AND URINARY EXCRETION OF CITRATE IN AN INFANT WITH RICKETS

A.S. AGE 18 MOS.

Day	P	*Serum* Ca *Mg./100 cc.*	*Cit.*	*Urine Cit. Mg./day*
1	3.0	8.9	1.9	
3				83
4				79
5				88
6	3.0	9.9	1.8	
7		*Vit. D, 600,000 units*		
8				108
9				115
10				155
11				151
14	4.6	10.6	3.3	
18	6.9	11.2	3.8	

In Figure 2 are summarized the results of similar studies of M. N., an eight-month-old rachitic infant. In this boy the concentrations of serum citrate before therapy were quite low, 1.2 and 1.3 mg. per 100 cc. Following the injection of 600,000 units of vitamin D the levels of serum citrate and of serum phosphorus increased slightly and the concentration of serum calcium rose. The concentrations of serum citrate and phosphorus did not, however, show the progressive increase seen in the previous patients and on x-ray there was little evidence of healing. Accordingly 25 days later a second injection of 600,000 units of vitamin D was given. The serum citrate level increased rapidly following this second dose to a maximum of 4.6 mg. per 100 cc. and the concentration of serum phosphorus likewise rose to levels compatible with the rapid healing of the rickets which was now evident by x-ray. The urinary excretion of citrate increased progressively after the first dose of vitamin D, but there was little further change following the second course despite the continued rise of serum citrate.

In Figure 3 are charted the concentrations of serum citrate of all ten infants with rickets arranged with respect to the time before or after the administration of vitamin D. One other infant besides patient M. N. (Fig. 2) showed little therapeutic effect following the first dose of 600,000 units of vitamin D, and a second dose of 600,000 units of vitamin D was given to produce complete healing. For these two patients the data are plotted with respect to the time of administration of the second course of vitamin

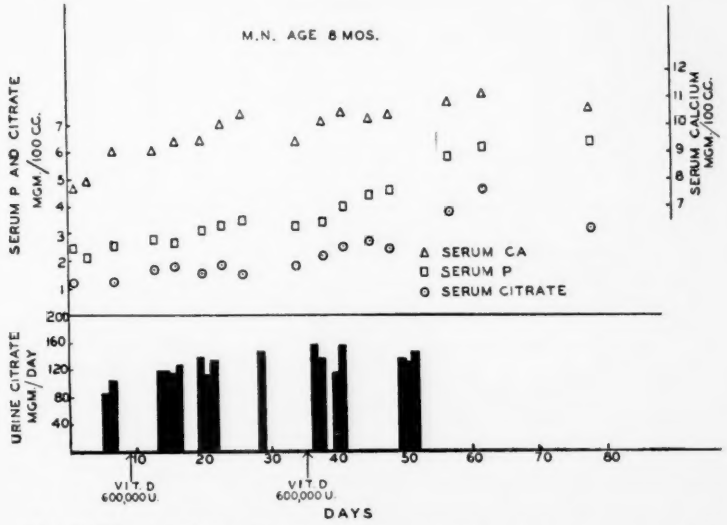


FIG. 2. Effect of vitamin D upon the urinary excretion of citrate, and upon the concentrations of citrate, phosphorus, and calcium in the serum of a rachitic infant, M. N., age 8 months. The urinary citrate is shown by the solid columns, serum citrate by ⊙, serum phosphorus by □, and serum calcium by △. The days on which vitamin D was injected are designated by the arrows.

D. The average value of 21 determinations of serum citrate in the ten rachitic patients before administration of any vitamin D was 1.5 ± 0.38 mg. per 100 cc. in comparison with the average value of 2.5 mg. per 100 cc. in the group of normal infants. This difference is statistically significant, $p < .01$. Following treatment with vitamin D the concentrations of serum citrate rose in all patients to values of 2.5 mg. or more. The rate of increase was variable so that in some instances a definite rise was found within five days, whereas in other cases ten or more days elapsed before the serum citrate rose to values above 2.0 mg. per 100 cc. In no instance was the level of serum citrate found to be low in a patient who showed evidences of healing of the rickets by x-ray. In several patients the concentration of serum citrate rose to levels above 3.5 mg. per 100 cc. and as high as 4.6 mg.

per 100 cc., which are above the normal range. These excessively high values of serum citrate are presumably evidences of temporary hypervitaminosis D, as they gradually dropped again to normal levels over a period of several months.

In order to see whether the levels of serum citrate were correlated with either the levels of serum calcium or of serum phosphorus, the concentra-

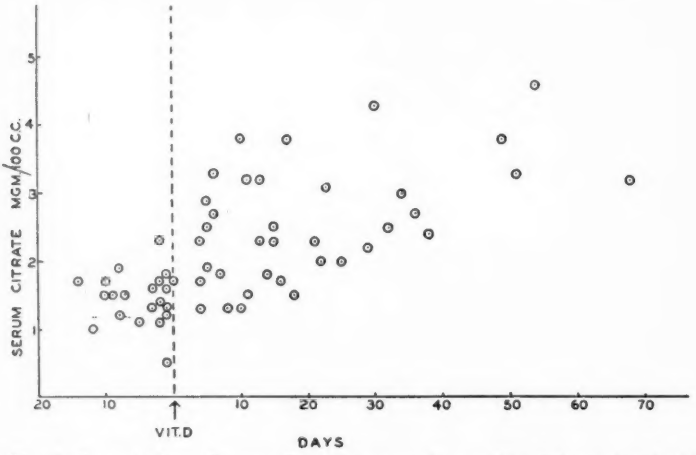


FIG. 3. Concentrations of serum citrate in group of ten rachitic infants plotted with respect to time before or following administration of vitamin D.

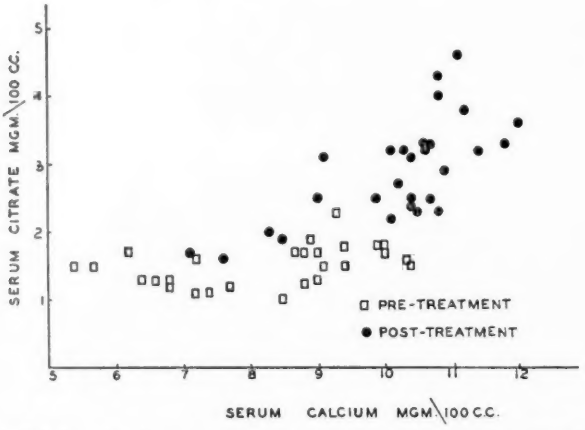


FIG. 4. Relationship of concentration of serum citrate to that of serum calcium in rachitic infants. Values before treatment with vitamin D shown by open squares, values following treatment with vitamin D by filled circles.

tions of serum citrate on the ordinate were plotted against the concentrations of serum calcium on the abscissa in Figure 4 and against the concentrations of serum phosphorus in Figure 5. The pre-treatment data are indicated by the open squares and the post-treatment values by the solid circles. Although in Figure 4 there is an apparent correlation between the concentration of serum citrate and that of serum calcium, closer analysis reveals that the data fall into two separate groups. There is no correlation between the levels of serum citrate and serum calcium before treatment, but

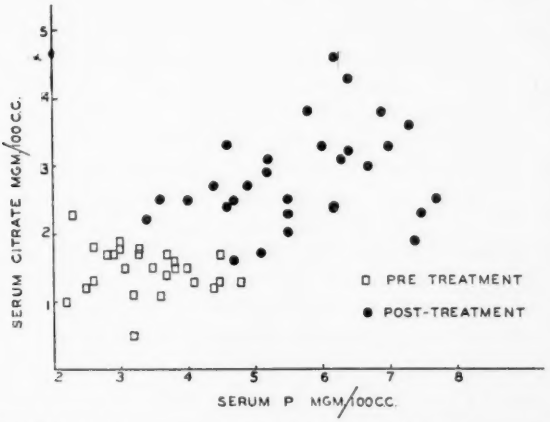


FIG. 5. Relationship of concentration of serum citrate to that of serum phosphorus in rachitic infants. Values before treatment with vitamin D shown by open squares, values following treatment with vitamin D by filled circles.

there is a rise of the concentration of serum calcium as well as of serum citrate after vitamin D. The data for the levels of serum citrate and serum phosphorus in Figure 5 show the same separation into two groups with no correlation between the concentrations of serum phosphorus and serum citrate in the pre-treatment group, whereas in the post-treatment group the increase of serum citrate is seen to be roughly parallel to the increase of serum phosphorus.

DISCUSSION

The data show unequivocally that the concentration of citrate in the blood serum and the urinary excretion of citrate are influenced by vitamin D. There are variations in the extent and the rate of rise in the levels of serum citrate following administration of a standard dose of vitamin D to infants and children with rickets. The intramuscular administration of total doses of 1,200,000 units of vitamin D to two children with rickets resulted in temporary rises of serum citrate to supernormal levels despite slow

response to an initial dose of 600,000 units. The essential problem is whether the effect of vitamin D on the level of citrate in the serum and the urinary excretion of citrate affords us a clue to the mode of action of vitamin D on tissue cells, or whether it is simply a phenomenon secondary to the effect of vitamin D on the levels of calcium and phosphorus in the body fluids.

In a recent review of the Krebs citrate cycle,[19] citrate is considered to be an integral link in the series of transformations of organic acids which are required for the oxidation of the "activated acetate" which is formed in the metabolism of protein, fat, and carbohydrates. Citrate is therefore continuously being formed and broken down in tissue cells, and the levels of citrate in the blood serum should reflect the balance of these processes in tissue cells. Temporary reductions of serum citrate follow the administration of glucose or the injection of insulin with subsequent return to the basal level.[15] Under *in vitro* conditions the synthesis of citrate is inhibited by addition of calcium,[13] but in the intact animal conditions which cause hypocalcemia are associated with reduction of serum citrate, and increase of the serum calcium is accompanied by increase of serum citrate. For example, it has been reported that in two patients with hypoparathyroid tetany the serum citrate was reduced to 1.3 and 1.6 mg. per 100 cc.,[1] whereas in two patients with hyperparathyroidism the serum citrate was elevated to 4.0 mg. per 100 cc. Shorr, *et al.*,[20] also reported a rough parallelism between urinary excretion of calcium and of citrate in a patient with hyperparathyroidism and in a subject with hypoparathyroidism given parathyroid extract. Since the metabolism of citrate has been studied in but few patients with disturbances of parathyroid function the results can only be considered as suggestive. In intact dogs an increase of serum citrate coincident with increase of serum calcium has been reported following administration of parathyroid extract.[1] Freeman and Chang[7] determined the concentrations of serum calcium and citrate of thyroparathyroidectomized dogs and found that the level of serum citrate was reduced as hypocalcemia developed. When large doses of vitamin D were given to these animals, the concentrations of serum citrate and of calcium both increased. All of these effects of parathyroid hormone and of vitamin D might be interpreted as indicating that the citrate levels of the body fluids are influenced by the concentrations of serum calcium, or, conversely, that the changes in the level of calcium in the serum produced by both parathyroid hormone and vitamin D are in some way related to effects of these agents upon the metabolism of citrate.

In the present studies on rickets there is a partial correlation between the levels of serum citrate and of serum calcium, but the data plotted in Figure 4 do not indicate a direct relation between the concentrations of total serum calcium and of serum citrate. In this diagram the points fall into two distinct groups. In the rachitic pre-treatment group the concentrations of serum citrate are low, ranging between 1 and 2 mg. per 100 cc., and there

is no correlation with the concentrations of serum calcium which vary between 5 and 10.5 mg. per 100 cc. Following treatment, the levels of both serum citrate and calcium rise so that there is a correlation between these two variables in the post-treatment group. These results suggest that the increased concentration of serum citrate following vitamin D is not the result of increase in the level of serum calcium but that both of these changes are manifestations of vitamin D effect. Similar comparison of the levels of serum inorganic phosphorus and of serum citrate reveals a correlation between these two variables, but separation of the data into pre-treatment and post-treatment groups again suggests that there is no direct relation between the concentrations of serum phosphorus and of serum citrate, but that the simultaneous increase of the levels of serum phosphorus and serum citrate following vitamin D therapy are both manifestations of vitamin D effect. It is possible, of course, that there may be changes in the concentrations of intracellular calcium or of organic phosphoric acid esters which may influence the metabolism of citrate, and that such variations in the intracellular state of calcium and phosphorus are not directly related to the concentrations of these ions in extracellular fluid.

There is a large body of data which show that the urinary excretion of citrate is influenced by the acid-base equilibrium of the body. Administration of alkali results in an increased excretion of citrate, whereas acidifying salts produce a decreased excretion of citrate. The acid-base ratio of the diet is of significance in the experimental rickets of rats. Certain neutral or alkaline ash diets which are not rachitogenic produce rickets when the acid intake is increased.[18] In the human variety of rickets due to vitamin D deficiency without abnormal ratios of calcium to phosphorus in the diet, there is no evidence of any disturbance of acid-base equilibrium which could account for the reduction of the concentration of citrate in serum and urine or for the increase in these values following vitamin D therapy.

The diet of the infants was composed chiefly of milk which contains about 0.16% citrate.[4] There is no direct evidence concerning the efficiency of absorption of dietary citrate, but it seems highly unlikely that increased absorption of citrate could explain the increase in serum citrate levels resulting from vitamin D therapy. When citrate is administered orally in large amounts it is rapidly utilized so that there is little increase in urinary excretion of citrate. Following oral or intravenous administration of citrate to normal subjects it is removed rapidly from the blood and the concentration of serum citrate returns to basal levels.[9] Persistent changes in the concentration of citrate in the serum probably indicate changes in the metabolic processes involved in the formation and transformation of citrate in the tissues.

The biochemical mechanisms involved in the interrelation of vitamin D and the metabolism of citrate and of calcium are unexplained. Further studies are in progress which may throw light on this problem.

Summary

Studies of citrate metabolism were made in ten rachitic infants. In this group the concentration of citrate in the serum was determined before and following the administration of vitamin D. In three infants measurements of the urinary excretion of citrate were also made and the effect of vitamin D studied.

The average level of serum citrate in the rachitic infants was found to be reduced to 1.5 mg. per 100 cc. in comparison with the average value of 2.5 mg. per 100 cc. in normal infants. Following intramuscular injection of either a single dose of 600,000 units of vitamin D or a total of 1,200,000 units in two injections the level of serum citrate rose progressively. In several infants the concentration of citrate in the serum increased following treatment to values above the normal range and then returned to normal levels. The urinary excretion of citrate increased following vitamin D treatment in each of the three infants studied.

The increase in concentration of citrate in the serum was found to coincide with the other manifestations of vitamin D effect which were studied, i.e., rise of the level of serum phosphorus, increase in the concentration of serum calcium, and healing of the bone lesions as demonstrated by x-ray examination.

References

1 Alwall, N.: IV. Studien über die Regulation vom Citronensäuregehalt des Blutserums. Acta med. scand., 1944, *116*, 337.

2 Alwall, N. and Nilsky, I.: III. Studien über die Regulation vom Citronensäuregehalt des Blutserums. Acta med. scand., 1944, *116*, 322.

3 Bodansky, A.: Phosphatase studies. II. Determination of serum phosphatase. Factors influencing the accuracy of the determination. J. Biol. Chem., 1933, *101*, 93.

4 Bridges, M. A. and Mattice, M. R.: *Food and beverage analysis*, 2d ed. Philadelphia, Lea and Febiger, 1942.

5 Dickens, F.: The citric acid content of animal tissues with reference to its occurrence in bone and tumor. Biochem. J., 1941, *35*, 1011.

6 Fiske, C. H. and Subbarow, Y.: The colorimetric determination of phosphorus. J. Biol. Chem., 1925, *66*, 375.

7 Freeman, S. and Chang, T. S.: Effect of thyroparathyroidectomy and vitamin D upon serum calcium and citric acid of normal and nephrectomized dogs. Am. J. Physiol., 1950, *160*, 341.

8 Freudenberg, E.: Die Stoffwechselwirkung des D-Vitamins Stosses bei Rachitis and Tetanie. Ann. paediat., Basel, 1939, *153*, 233.

9 Hagelstam, L.: Über den Wert der Citronensäurebestimmungen in Blutserum fur die Differentialdiagnose bei Erkrankungen dem Leber und der Gallenwege. Acta chir. scand., 1944, *90*, 37.

10 Hamilton, B. and Dewar, M. M.: Effect of citrate and tartrate on experimental rickets. Am. J. Dis. Child., 1937, *54*, 548.

11 Hastings, A. B., McLean, F. C., Eichelberger, L., Hall, J. L., and DaCosta, E.: The ionization of calcium, magnesium, and strontium citrates. J. Biol. Chem., 1934, *107*, 351.

12 Kramer, B. and Tisdall, F. F.: A simple technique for the determination of calcium in small amounts of serum. J. Biol. Chem., 1921, *47*, 475.

13 Martius, C. and Lynen, F.: Probleme des Citronensäurecyclus. Advances in Enzymology, 1950, *10*, 167.

14 Natelson, S., Pincus, J. B., and Lugovoy, J. K.: Microestimation of citric acid: a new colorimetric reaction for pentabromacetone. J. Biol. Chem., 1948, *175*, 745.

15 Natelson, S., Pincus, J. B., and Lugovoy, J. K.: Response of citric acid levels to oral administration of glucose. I. Normal adults and children. J. Clin. Invest., 1948, *27*, 446.

16 Nicholaysen, R. and Nordbo, R.: Calcium metabolism and citric acid. Acta physiol. scand., 1943, *5*, 212.

17 Shohl, A. T.: The effect of the acid-base content of the diet upon the production and cure of rickets with special reference to citrates. J. Nutrit., 1937, *14*, 169.

18 Shohl, A. T., Brown, H. B., Chapman, E. E., Rose, C. S., and Sauerwein, E. M.: Rickets in rats. XIV. A diet which demonstrates the effect of the acid-base content upon the production of rickets and also idiopathic tetany. J. Biol. Chem., 1932, *98*, 215.

19 Shohl, A. T. and Butler, A. M.: Citrates in the treatment of infantile rickets. N. England J. M., 1939, *220*, 515.

20 Shorr, E., Almy, T. P., Sloan, M. H., Taussky, H., and Toscani, V.: The relation between the urinary excretion of citric acid and calcium: its implications for urinary calcium stone formation. Science, 1942, *96*, 587.

VARIATIONS IN THE GAG, COUGH, AND SWALLOW REFLEXES AND TONE OF THE VOCAL CORDS AS DETERMINED BY DIRECT LARYNGOSCOPY IN NEWBORN INFANTS*

HERBERT C. MILLER,** G. O'NEIL PROUD, AND FRANKLIN C. BEHRLE

This investigation is part of a comprehensive effort to determine the degree of vagal function in newborn infants. No particular attention has been given to this problem previously, but in the light of recent experimental work in animals there is a clear indication for such a survey in newborn infants.

The presence of an effective vagal mechanism is essential to the life of newborn kittens and puppies, but the adults of these species can survive vagal deprivation indefinitely, such as results when the vagi are cut in the midcervical region.[8] Vagotomy in rabbits performed in the above manner results in pulmonary edema and death within a few hours. Recently it has been shown that in addition to the pulmonary edema, hyaline membranes are formed in the alveoli and alveolar ducts of the lungs of rabbits[10] and puppies,[1] the only species examined to the present time. These pulmonary hyaline membranes are similar in appearance and have the same histochemical properties as those found in the lungs of newborn infants dying in the first few hours and days after birth.[2] It was this observation which led us to investigate the rôle of the vagus in newborn infants.

Some evidence already exists for believing that vagal function is not fully developed in newborn infants. Wiggers has stated: "To judge from the rapid [heart] rate in infancy, its gradual decrease during childhood, and the fact that atropin does not accelerate it in children, the vagus influence has not developed in early life, but is acquired gradually."[13] Hoff writes: "In infancy and in old age (man), vagal 'tone' is at a minimum, while it is at a maximum during adolescence and early adulthood."[5] Vagal influence on the gastrointestinal tract also appears to be minimal at this age, as indicated by the relatively reduced peristaltic activity[9] and the low output of hydrochloric acid by the stomach when compared to older infants.[4] Miller and Behrle have shown that vagal control of respiration apparently is not fully developed, particularly in premature infants.[11] In view of these observations it seemed important to obtain additional information concerning vagal function in the newborn period.

---

* From the Departments of Otolaryngology and Pediatrics, University of Kansas Medical School, Kansas City, Kansas.
** Resident in Pediatrics, New Haven Hospital, 1937-1938.
Received for publication December 1, 1951.

One of the important rôles of the vagus nerves is to help maintain the reflexes in the pharynx and larynx which produce coughing, swallowing, and gagging. While there are generalized statements in most pediatric texts to the effect that these reflexes are sometimes diminished or even absent in some newborn infants, particularly premature infants, no record could be found of any systematic study of them. The nearest approach to an evaluation was that made by Flagg on the action of the vocal cords in newborn infants. He described a loss of tone and a failure of the vocal cords to go into spasm on direct laryngoscopy in asphyxiated newborn infants.[5] He stated that reflex spasm of the glottis was a more sensitive reflex than that of the cornea in the dying infant, but did not extend his observations

TABLE 1

INCIDENCE OF COUGH REFLEX DETERMINED BY DIRECT LARYNGOSCOPY IN INFANTS ACCORDING TO AGE

	Age of infants				
Group	0-4 *days*	5-9 *days*	10-30 *days*	*Over* 1 *month*	*Total*
Premature	17	5	3	4	29
Cough reflex	7	0	0	1	8
%	41	0	0	25	27
Full-term	63	33	8	21	125
Cough reflex	17	19	6	19	61
%	27	57	75	90	49

to include other reflexes.[6] Consequently, in the present study a routine examination of a series of newborn and older infants was made by means of direct laryngoscopy, with particular attention being paid to the position of the vocal cords and their action and to the presence or absence of the gag, swallow, and cough reflexes. All the laryngoscopies were done by one of us (G.O.P.) by direct visualization. The gag and swallow reflexes were noted with the introduction of the laryngoscope into the pharynx. After the position and action of the vocal cords were determined, the presence or absence of the cough reflex was ascertained by squirting a few drops of normal saline on to the vocal cords by means of a syringe and needle while the laryngoscope was in place. Any cough resulting from either the introduction of the scope or following the squirting of saline on the vocal cords was considered as a positive result.

RESULTS

Direct laryngoscopies were done on 154 infants. All but two of these had gag and swallow reflexes. The histories and findings in these two infants will be detailed later, along with those of a third infant who was laryngoscoped on five different occasions during the first 63 days of life.

A cough reflex could not be obtained in over half the infants tested. The lowest incidence was found in the more immature infants and younger infants. As shown in Table 1, there were only 8 out of 29 premature infants, or 27 per cent, with cough reflexes, while 61 out of 125 full-term infants, or 49 per cent, had cough reflexes. The incidence in full-term infants rose from 27 per cent in the first 5 days of life to 57 per cent in the second 5 days, 75 per cent in infants 10 to 30 days of age, and 90 per cent in infants 2 to 11 months old.

The failure to obtain a cough in a large group of infants led us to determine the incidence of a spontaneous cough reflex immediately following delivery. The obstetrician was asked to record the presence or absence of a cough while the baby remained in the delivery room. The results are shown in Table 2. There were 167 infants observed and 72 or 43 per cent of these coughed spontaneously. Six of 18 premature infants and 66 of 149

TABLE 2

INCIDENCE OF SPONTANEOUS COUGH IN NEWBORN INFANTS

		Birth weight	
	Infants no.	*2,500 gm. or less*	*2,501 gm. or more*
Total infants	167	18	149
Cough present	72	6	66
%	43	33	44

full-term infants had a spontaneous cough at birth. A higher incidence of spontaneous coughing was obtained at birth than was found by direct laryngoscopy in the first 10 days of life, suggesting that possibly the test situations were not valid. Consequently, 40 of the infants on whom observations had been made for the presence or absence of a spontaneous cough reflex at birth were also examined with the laryngoscope during the first 7 days of life. Five infants who coughed spontaneously at birth responded with a cough when laryngoscoped; 17 infants who did not have a spontaneous cough at birth did not respond with a cough when tested later; 2 infants who did not cough spontaneously at birth responded positively to the laryngoscopic examination; 16 infants who had a spontaneous cough at birth did not cough when tested after birth by laryngoscopy, 15 of the 16 negative responses occurring within the first 4 days after birth. During this same period there was a high degree of correlation between the cough response obtained when the laryngoscope was introduced into the throat and to the saline squirted onto the vocal cords (Table 3). It can be seen that the responses were similar in 41 of the 45 infants who were under five days of age. Among the infants 5 to 9 days of age the number of agreements dropped to 12 out of 21 tests; this was at a time when the incidence of positive responses was increasing. A further change occurred among the

infants 10 to 30 days old, for the number of agreements increased to 9 out of 12 infants. These data do not permit a conclusion concerning the cause of the higher incidence of spontaneous cough immediately following birth as compared to that found in the first four days of life.

The position and action of the vocal cords was noted in all but two of the 154 infants examined with the laryngoscope. The response in 146 infants to the introduction of the laryngoscope was a quick and vigorous snapping together of the vocal cords, as described by Flagg. In the six remaining infants the vocal cords were bowed, lacked tone, or adducted poorly. The cough reflex was absent in five of the six infants. Four of the six infants appeared to be healthy in all respects; one was a premature infant whose birth weight was 2,150 grams and who was examined on the day of birth;

TABLE 3

COUGH RESPONSE TO LARYNGOSCOPE COMPARED TO THAT WITH SALINE ACCORDING TO AGE OF THE FULL-TERM INFANTS

Infants responding to		*Number of infants by age*		
Laryngoscope	*Saline*	0-4 *days*	5-9 *days*	10-30 *days*
0	0	39	6	3
+	+	2	6	6
+	0	2	4	3
0	+	2	5	0
TOTAL		45	21	12

the other three infants had birth weights of 2,540, 3,500 and 3,250 gms., respectively, and were 1, 2, and 4 days of age when examined. The absent cough reflex was the only other significant finding in these four infants. A fifth infant was born prematurely and died on the second day; the history and findings are recorded in detail in Case 2. The sixth infant with bowed vocal cords was four months old and had laryngeal stridor and a meningocele; the cough reflex was present in this infant.

Three infants had findings on laryngoscopic examination which were sufficiently different from the others as to warrant a more detailed description of their courses and findings. All were premature infants. Two of these infants died on the second day of life and the third survived. Their case summaries are given below.

Case 1. Baby M. Hosp. no. 51-2570. This male infant was born at 9:00 P.M. on 3/26/51 after an uneventful pregnancy to a mother who was a para two. Immediately after birth the respirations were poor and there was considerable sternal retraction. Fifteen minutes after birth he became apneic, but respirations were re-established within 10 minutes, using oxygen and artificial respiration. A small amount of mucus was suctioned from the pharynx at this time. Sternal retraction became deeper. He was put in an incubator and received added oxygen constantly. The respirations con-

tinued to be regular with deep retractions on each inspiration for the next 9 hours. At 12 hours of age he was apneic and became cyanotic. Following his revival, the baby had a convulsion. A direct laryngoscopy was done at 13 hours of age, at which time the color was improved. It was found that the cords abducted well but did not meet in the midline on phonation. The cords lacked tone and were slightly bowed. No cough, gag, or swallow reflex could be obtained. The epiglottis was normal in size and position. Following the laryngoscopy the baby continued to breathe with deep sternal retraction and remained slightly cyanotic. Death occurred 20 hours after birth and 7 hours after the laryngoscopy. Autopsy revealed atelectasis with light interstitial pneumonitis and a subarachnoid hemorrhage over the inferior surface of the cerebellum and medulla.

Case 2. Baby J. Hosp. no. 51-3170. Baby was born at home after an uneventful pregnancy. He was brought to the hospital one-half hour after birth. The weight of the infant was 1,440 grams. He was dusky in color and respirations were feeble but improved when the pharynx was suctioned. There was moderate subcostal retraction. He was placed in an incubator and given oxygen continuously and penicillin parenterally. At 12 hours of age the breathing was regular and the lower portion of the chest retracted as the upper portion expanded and as the diaphragm contracted. A direct laryngoscopy was done at 18 hours of age when the color was good. No gag reflex was obtained when the laryngoscope was introduced into the pharynx. The swallow reflex was feeble. The vocal cords were not visualized and no cough reflex was elicited. The infant died 36 hours after birth and 18 hours after the laryngoscopy. Autopsy showed atelectasis, hyaline membranes in the lung, and a subdural hemorrhage around the brain stem.

Case 3. Baby R. Hosp. no. 51-25143. This male infant weighing 1,505 gm. was born on 2/21/51 to a gravida 4, para 2, after an uneventful pregnancy and labor. Following its birth, the baby was apneic for a few minutes. There was much mucus aspirated from the nose and throat. Respirations began with use of a respirator which provided alternating positive and negative pressures through a face mask. The color remained dusky for a period of two hours following delivery, but improved gradually thereafter. The infant was placed in an incubator provided with oxygen. Twenty-four hours later the baby's color was good and respirations were adequate. Oxygen was given continuously for the first 10 days of life. The lowest weight was 1,275 gm. on the seventh day. Weight gain was steady and satisfactory from then on, although the baby did not swallow its milk easily at any time during the first six weeks. Laryngoscopy was done on the 28, 44, 46, 55, and 63 days of life. The gag and swallow reflexes were always present, but no cough reflex was obtained except on the 55th day. On the 27th day of life the infant choked and was found to be cyanotic and apneic. What appeared to be milk was removed from the pharynx by suction. Artificial respiration and oxygen were given and the infant began to revive. The infant had choking spells later in the day and again on the 31st and 33d days. A roentgen examination of the chest on the day following the first choking spell showed a complete opacity of the right upper lobe, which had disappeared six days later. No fever was present at any time; there was a temporary weight loss of 2 ounces on the 27th day of life, but a steady weight gain thereafter. The infant was discharged on the 63d day weighing 2,950 gm. in good health.

Discussion

The cough reflex is most commonly initiated by the stimulation of vagal afferent nerve endings in the mucosa of the larynx and trachea, although there are some fibers of the glossopharyngeal nerve in the pharynx which are capable of being stimulated as well as a branch of the vagus (Arnold's

nerve) to the ear. As a result of the sensory stimulation, the vocal cords close and the intrapulmonary pressure is suddenly increased by a spasmodic expiratory effort. The sudden release of the vocal cords and intrapulmonary pressure allows material to be moved cephalad in the respiratory tract. The data obtained by the present investigation do not give any clue as to the explanation for the large number of newborn infants without a cough reflex. The lack of a cough reflex could be accounted for by either an absence of afferent sensory stimuli or a failure to develop a sudden, spasmodic expiratory effort. Recent work by Miller and Behrle on the vagal control of respiration suggests that some newborn infants, particularly premature infants, behave in respect to breathing as though the afferent stimuli were not being transmitted from the lungs to the medullary centers.[11] This would tend to support the theory that the major factor in the absence of the cough reflex was the lack of sensory stimulation.

The high degree of correlation between the response to the introduction of the laryngoscope and to the squirting of water on the vocal cords in the first five days of life, and again at a later age when the cough reflex was obtained with high frequency, suggests that the test situation was valid. The relative lack of correlation between the results of these two tests during the age period of five to ten days may be explained by the fact that the incidence of the positive responses was rapidly increasing. There can be no gainsaying the fact that the squirting of saline onto the vocal cords was in itself a severe test. It is almost certain the saline reached beyond the vocal cords to include the mucosa of the trachea and its bifurcation. The higher incidence of spontaneous cough at birth compared to that found in the first five days of life may represent an actual difference rather than merely a change in the test situation. In this connection it is interesting to note that the secretion of HCl acid in the stomach, which is also under vagal influence, is notably greater the first week of life than in the days that follow.[12] Miller and Behrle have also noticed a greater regularity in respiration during the first day of life than is subsequently found, suggesting that perhaps vagal function undergoes some diminuition following birth.

It is interesting to speculate about the significance of the absence of the cough reflex at birth. Even in those infants in which it was present, it was notable that the response was brief and weak, amounting to rarely more than one short, slight spasmodic effort. It would seem likely that the cough reflex must be absent or diminished greatly during uterine existence and this might allow amniotic fluid to enter the trachea and other portions of the bronchial tree, especially if ciliary activity and the bechic reflex were unable to cope with the entering fluid. There has been considerable divergence of opinion as to the good or bad effects of amniotic fluid in the lung. Most observers agree that practically all lungs of stillborn and newborn infants contain fluid when examined at autopsy. There is also general agreement that small amounts of amniotic fluid can be of little harmful

consequence. The belief continues that large amounts of amniotic fluid may prevent expansion of the lungs, although the direct evidence to support this theory is lacking. Gruenwald has shown that the lungs of newborn infants and stillborn infants can be expanded with half the pressure if saline is used as compared to air alone.[7] Behrle, Gibson, and Miller found that lungs which contained large amounts of amniotic fluid required no more pressure and expanded as easily as lungs that were free of foreign materials.[2] It seems plausible to believe that the admission of fluid to the unexpanded lung may be beneficial in reducing surface tension and hence in making it possible to expand the lung with reduced pressures. It remains to be proven that large amounts of amniotic fluid are harmful. The absent or diminished cough reflex may be significant in permitting access of amniotic fluid to the lung prior to birth.

The long-continued depression or absence of the cough reflex in premature infants, as demonstrated in Case 3, may be the cause of the frequent respiratory difficulties seen in premature infants. Perhaps part of the susceptibility of the premature infant and full-term infant to staphylococcal pneumonia may be related to the absence of the protective influence of the cough reflex in keeping out of the lung the pharyngeal contents, among which pathogenic strains of staphylococci are commonly found.

It is not clear that asphyxia is the only factor controlling the action of the vocal cords in newborn infants as Flagg indicated. Several infants were examined who showed no evidence of asphyxia and yet the tone of the vocal cords was less than expected. The striking absence of the gag, swallow, and cough reflex as well as the atonic condition of the cords in Case 1 and the lack of a gag and cough reflex in Case 2 perhaps were caused by the asphyxia of the infants, but neither of the infants was very cyanotic at the time of the laryngoscopy and neither was in a critical condition. An alternative hypothesis can be made out in the light of the present findings regarding the cough reflex and the increasing awareness that the vagal reflexes controlling other vital functions are not fully developed. It would seem quite possible that the reflexes in these two infants were not obtained because of a failure of development somewhere along the reflex arc. Further observations in which the state of the reflexes are correlated with the clinical conditions and autopsy findings are needed in order to settle this point.

Summary

Direct laryngoscopies were done on 154 infants from birth to eleven months of age. A cough reflex could be obtained in only about one-quarter of the infants during the first five days of life, but in infants over a month of age the cough reflex was present in 90 per cent. One premature infant repeatedly examined developed no cough until the 55th day of life. The gag and swallow reflexes were present in all but two infants, both of whom

were premature and failed to survive the second day of life. The vocal cords were bowed and had diminished tone in six infants, four of whom showed no signs of asphyxia at any time. The relationship between the findings in the present study and a possible immaturity of vagal function has been discussed.

References

1 Behrle, F. C., Gibson, D. M., and Miller, H. C.: Presence of hyaline membrances in vagotomized puppies. (Unpublished work.)

2 Behrle, F. C., Gibson, D. M., and Miller, H. C.: Rôle of hyaline membranes, blood, exudate, edema fluid and amniotic sac contents in preventing expansion of the lungs of newborn infants. Pediatrics, 1951, *7*, 782.

3 Coombs, H. C. and Pike, F. H.: The nervous control of respiration in kittens. Am. J. Physiol., 1930, *95*, 681.

4 Cutler, R. D.: The normal gastric secretion of infants and small children following stimulation with histamine. J. Pediat., S. Louis, 1938, *12*, 1.

5 Flagg, P. J.: Asphyxia neonatarum. Surg. Gyn. Obst., 1938, *67*, 153.

6 Flagg, P. J.: Treatment of asphyxia in the newborn. J. Am. M. Ass., 1928, *91*, 788.

7 Gruenwald, P.: Surface tension as a factor in the resistance of neonatal lungs to aeration. Am. J. Obst., 1947, *53*, 996.

8 Hoff, H.: Page 666 in: Fulton, *Textbook of physiology*. Philadelphia, W. B. Saunders Co., 1950.

9 Ivy, A. C.: Page 5 in: Brennemann, *Practice of pediatrics*, Vol. I. Hagerstown, Md., W. F. Prior Co. Inc., 1937.

10 Miller, H. C., Behrle, F. C., and Gibson, M. D.: Comparison of pulmonary hyaline membranes in vagotomized rabbits with those in newborn infants. Pediatrics, 1951, *7*, 611.

11 Miller, H. C. and Behrle, F. C.: Control of respirations in newborn infants as determined by air flow and pneumographic studies. (To be published.)

12 Smith, C. A.: Page 306 in: Mitchell-Nelson, *Textbook of pediatrics*. Philadelphia, W. B. Saunders Co., 1950.

13 Wiggers, C.: Page 221 in: Abt, *Pediatrics*, Vol. IV. Philadelphia, W. B. Saunders Co., 1923.

STUDIES IN CONGENITAL CARDIOVASCULAR DISEASE

IV. Impaired Pulmonary Diffusion of Oxygen in Persons with Left-to-Right Shunts*

NELSON K. ORDWAY**

Studies of patients with congenital heart disease in which there is a left-to-right shunt have revealed, in about 15%, arterial unsaturation which is completely alleviable by the administration of oxygen. The response to oxygen shows that all the venous blood of these individuals passes through functioning pulmonary tissue; if any blood were shunted back into the systemic circulation in such a way as to escape oxygenation in the lungs, complete saturation of arterial blood could not occur. In this report there will be presented anatomical and physiological reasons to believe that the anoxemia experienced by these patients lies in impaired diffusion of oxygen at the pulmonary alveolar-capillary level. The disturbance in two subjects was sufficient to produce clinical cyanosis, a feature which in Abbott's time-honored classification of congenital heart disease[1] implies the existence of a right-to-left shunt. The demonstration in this report of the frequent existence of arterial anoxemia in subjects with congenital heart disease without a right-to-left shunt points to the desirability of restating Abbott's classification in terms of altered physiology rather than clinical appearance.

Plan of Study

Clinical material. The subjects were patients studied at New Haven in 1946 and 1947 and in New Orleans in the years 1948 to 1951. All the children were examined by the author. Except in the case of a few patients with unusual, bizarre anomalies, the clinical diagnoses were usually not difficult, and in most instances were supported by cardiac catheterization or operation. No patient with known or suspected parenchymatous pulmonary disease is included.

Techniques. Arterial puncture was carried out in all patients, using the unexposed radial, brachial, or femoral artery. Cardiac catheterization, performed in most of the patients, was usually accomplished via an antecubital vein, occasionally by way of the external jugular, or the saphenous close to its junction with the femoral.

---

* From the Departments of Pediatrics of the Louisiana State University School of Medicine and Yale University School of Medicine, and the Heart Station of Charity Hospital of Louisiana at New Orleans. This investigation was supported in part by research grants from the James Hudson Brown Memorial Fund of the Yale University School of Medicine, and from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

Some of this material was presented at meetings of the Society for Pediatric Research at Stockbridge, Massachusetts, May 12, 1947, and Atlantic City, New Jersey, May 4, 1949.

** Interne in Pediatrics, New Haven Hospital, 1938-1939.

Received for publication December 15, 1951.

Arterial samples were removed during the inhalation of air and of 100% oxygen. Oxygen was administered by a closely fitting mask covering the nose and the mouth,* at such a rate that the reservoir bag was kept constantly distended. The adequacy of exclusion of air during the oxygen inhalation was later checked by observation of a low N_2 reading in the blood oxygen analysis.

Both "air" and "oxygen" samples were removed during rest and during or immediately following muscular exercise. Exercise was accomplished in older patients by their running or jumping immediately before arterial puncture, or by pedaling a bicycle wheel while lying supine with the arterial needle in place. A similar state of activity was provided in infants by their crying and struggling incident to arterial puncture. The degree of exercise was not quantitated, but activity was ordinarily continued until the patient became short of breath.

The subjects were quiet during catheterization. Light anesthesia with intravenous thiopental (Pentothal®) or secobarbital (Seconal®) sodium was employed at the time of catheterization in several of the young children. Simultaneous withdrawal of arterial and intracardiac samples has been accomplished in the more recently studied patients. More than half, however, of the subjects reported had arterial puncture and venous catheterization carried out at separate times.

Blood samples were taken directly into syringes containing 10% potassium oxalate solution and were kept iced pending duplicate analysis for oxygen content by a modified Roughton-Scholander technique.[15] The analysis of arterial blood samples obtained during the inhalation of 100% oxygen was commenced within twenty minutes of collection. Oxygen capacity was determined gasometrically in at least two of the samples obtained from each patient. The optical density of all samples, observed as oxyhemoglobin or alkaline hematin, was determined in duplicate in the Evelyn photo-electric colorimeter. The relation between values for oxygen capacity and optical density determined on the same sample was expressed as a constant, which was used to calculate the oxygen capacity of samples on which only optical density had been determined. Adjustment was made for variation in oxygen content brought about by hemoconcentration or hemodilution indicated by variation in oxygen capacity. No correction has been made for the 2% dilution of each sample by the oxalate anticoagulant.

Definitions and Calculations

The following expressions and symbols will be used in this paper:

Oxygen content is total oxygen per 100 cc. of whole blood, including that carried in physical solution.

Oxygen capacity is the oxygen combining power of the hemoglobin in 100 cc. of whole blood, exclusive of oxygen carried in physical solution.

Oxygen saturation is the ratio of oxygen content minus dissolved oxygen to oxygen capacity. The normal range by the technique used was observed in children breathing air at rest to be 91 to 96%, with an average value of 93.1%.[16]

d_{O_2} is physically dissolved oxygen in pulmonary capillary blood during the inhalation of 100% oxygen. In the subject without a right-to-left shunt, pulmonary capillary blood is the same as systemic arterial blood. d_{O_2} is determined by subtracting the oxygen capacity of pulmonary capillary blood from its content during the inhalation of 100% oxygen. The normal range by the technique used, as determined in 13 children, was 0.6 to 1.7 volumes per 100 cc., with an average of 1.09 volumes per 100 cc.[16]

* O.E.M. No. 710 Nasal Meter Mask and O.E.M. No. 720 Oro-Nasal Meter Mask without oxygen concentration meter (O.E.M. Corporation, Fitch Street, East Norwalk, Connecticut).

l is the fraction of pulmonary capillary blood which appears *not* to be saturated with oxygen. It is equal to the difference between the observed percentage saturation and 100%, divided by 100. In the individual without a right-to-left shunt l is thus apparent from the percentage saturation of arterial blood. In the person with a right-to-left shunt l is calculated by a formula including six values: oxygen content, oxygen capacity, and dissolved oxygen, each during the inhalation of air and of 100% oxygen.[9] In the person with normal pulmonary respiratory function breathing air, l does not exceed 0.09, a value corresponding to the lower limit of normal arterial oxygen saturation, 91%. A value of 0.10 is accepted as being within normal limits when the indirect calculation is used. Values in excess of this limit indicate impaired transfer of oxygen from the outside air into pulmonary capillary blood. If pulmonary ventilatory function is normal (e.g., freedom from emphysema), a high value for l indicates impaired diffusion of oxygen across the alveolar-capillary membrane.

Arteriovenous oxygen difference is included in the tables because it is inversely proportional to systemic blood flow, of which it thus gives an approximation.

Pulmonary capillary flow factor, Λ, is the ratio of pulmonary capillary flow to systemic blood flow. Normally the two are equal ($\Lambda = 1.0$). When an uncomplicated left-to-right shunt is present, pulmonary capillary flow is increased ($\Lambda > 1.0$). In the presence of an uncomplicated right-to-left shunt, pulmonary capillary flow is decreased ($\Lambda < 1.0$).

Net right-to-left shunt, α, is the fraction of systemic venous return to the heart that is shunted back into the systemic circulation without passing through functioning pulmonary tissue. α is, of course, normally zero.

The tabulations to follow contain values for α, l, and Λ calculated according to appropriate equations which appear in previous reports.[9, 10] The equations include values for the oxygen content of blood acquired by needle or catheter from various vessels and heart chambers, and presuppose constancy of the circulation and completeness of mixing. Actually, even in normal persons it is frequently not possible to be sure of representative sampling, and in patients with shunts, difficulties of interpretation are greatly multiplied. Large differences in blood oxygen content at successive cardiac levels are necessary for the demonstration of left-to-right shunts, and consistency of multiple observations is required if reliance is to be placed on calculations of the magnitude of shunts. Within these limitations the data to be presented are acceptable.

Diagnostic considerations

Sixty-two patients with left-to-right shunts were studied. In 61 the shunts were congenital in origin (Table 1). In the remaining patient the left-to-right shunt was produced by operation.

All 16 cases of atrial septal defect* were confirmed at catheterization, and in six the catheter passed through the defect. The characteristic physical signs of mitral

* The designation, "atrial septal defect," refers to a defect through which blood is shunted from left to right only. "Large atrial septal defect," a term to be employed later, connotes a defect so large that shunts occur both from left to right and from right to left, resulting in more or less complete mixing of systemic and pulmonary venous streams.

stenosis led to the diagnosis of Lutembacher's complex in six of the total group. Of those with Lutembacher's complex only one gave a history of rheumatic fever.

Ventricular septal defect was diagnosed in 15 cases, in 12 of which it was demonstrated by catheterization. In seven of the catheterized subjects, however, the shunt was so small that the changes in intracardiac oxygen content approach the variability seen in normal persons. The pattern of changes in oxygen content in multiple samples was, however, consistent, and all these cases had a typical, loud, harsh, blowing systolic murmur at the third, fourth, or fifth left intercostal space close to the sternum, usually accompanied by a thrill. Two infants, age 13 months and 6 months (the latter is patient 4 in Table 3), were not catheterized but presented the typical findings of severe ventricular septal defect in infancy, with small body size, large heart and pulmonary vessels, typical thrill and harsh systolic murmur in the fifth left interspace close to the sternum, and a low pitched, apical, diastolic murmur. Patient 6 was catheterized, but the catheter failed to advance beyond the right atrium; at this level there was no evidence of left-to-right shunt. He gave a history of a heart murmur present at birth and had moderate exertional dyspnea. There was a long, harsh, blowing systolic murmur all over the precordium, loudest at the base. X-rays showed cardiac enlargement, fulness of the pulmonary artery, and some prominence of the lung vessels. Electrocardiogram showed right ventricular hypertrophy or right bundle branch block. Although the clinical features are not typical, failure to establish the presence of an atrial septal defect makes ventricular septal defect the most likely diagnosis.

Eighteen patients had patent ductus arteriosus. Its presence was confirmed at operation in 15 patients, and by cardiac catheterization in an additional two. In these and the one non-operated, non-catheterized subject the clinical findings of patent ductus arteriosus were characteristic.

Aortic septal defects were probably present in two patients who had ligation of small ducti but continued to show findings characteristic of patent ductus arteriosus. One child was catheterized postoperatively and persistence of a shunt at the level of the pulmonary artery was demonstrated.

In ten cases a right-to-left shunt was shown by arterial blood analysis to be present in addition to the left-to-right. These included three patients with large atrial septal defects; three with Eisenmenger's complex, one of whom had an associated atrial septal defect; three diagnosed as the Taussig-Bing complex[19] with atrial septal defect; and one diagnosed as having partial transposition of the great veins. The anatomical diagnosis is believed to have been confirmed by catheterization in nine cases and was shown at autopsy in the tenth.

One case, a four-year-old boy with the tetralogy of Fallot not included in Table 1, had a left-to-right shunt produced by a Potts-Smith-Gibson aorticopulmonary anastomosis.[15]

Physiological Observations

Impaired pulmonary diffusion of oxygen was demonstrated in eleven of the 62 patients. The diagnoses in 10 cases are indicated in Table 1.

Patients with normal pulmonary diffusion of oxygen

Observations made in 44 patients with left-to-right shunts, no right-to-left shunt, and normal pulmonary diffusion of oxygen are summarized in Table 2.

The absence of right-to-left shunt was proved by normal arterial oxygen saturations while breathing air, and normal differences between arterial

oxygen content and capacity while breathing 100% oxygen. In one four-year-old boy with patent ductus arteriosus a saturation of 90.4% was observed at rest but it rose to 94% on exercise. This is the only instance in this group of a value below 91%, the presumptive lower limit of normal arterial saturation by the technique used.

Normal pulmonary diffusion of oxygen was shown by the normal values for arterial oxygen saturation while breathing air.

In this group of patients, exercise, while frequently producing a change from the resting value, never produced an abnormal arterial oxygen saturation.

TABLE 1

AGE RANGE, DIAGNOSIS, AND PRESENCE OF IMPAIRED PULMONARY DIFFUSION OF OXYGEN IN 61 PATIENTS WITH LEFT-TO-RIGHT SHUNTS*

Diagnosis	*Age*		*Total number*	*Number with impaired pulmonary diffusion of oxygen*
	Range	*Number 16 years and younger*		
Atrial septal defect	8 mos.—42 yrs.	8	10	1
Lutembacher's complex	7—35 yrs.	1	6	2
Ventricular septal defect	6 mos.—26 yrs.	12	15	3
Patent ductus arteriosus	15 mos.—26 yrs.	13	18	1
Aortic septal defect	4—8 yrs.	2	2	0
Concomitant right-to-left shunt	17 mos.—58 yrs.	4	10	3
Totals			61	10

* This table includes ten patients previously reported by Ordway, Griffiths, and Nixon,[12] and three patients reported by Hyman, Levy, Bagnetto, and Ordway.[8]

The figures for arteriovenous oxygen difference indicate that no patient exhibited marked deviation of systemic blood flow from normal values.

Pulmonary capillary flow was on the average considerably increased and in only nine instances was it less than 1.8 times the systemic blood flow. Seven of these nine cases were patients with ventricular septal defects.

Patients with concomitant left-to-right and right-to-left shunts who showed normal pulmonary diffusion of oxygen present a special problem because of the presence of (i) right-to-left shunts ranging from 14 to 77% of the systemic venous return to the heart, (ii) responses to exercise which are not comparable with those of patients without a right-to-left shunt, (iii) reduced systemic blood flow evidenced by wide arteriovenous oxygen differences, (iv) only slightly elevated or actually reduced pulmonary capil-

lary flow, and (v) uniformly very high pulmonary arterial pressures. *l* was calculated to range from 0.08 to 0.04, indicating pulmonary capillary oxygen concentrations of 92 to 96%. This group will be presented in detail in a forthcoming publication.[11]

TABLE 2

SUMMARY OF OBSERVATIONS ON 44 PATIENTS WITH LEFT-TO-RIGHT SHUNTS, ABSENCE OF RIGHT-TO-LEFT SHUNT, AND NORMAL PULMONARY DIFFUSION OF OXYGEN

	Number of observations	*Range*	*Mean*	*Standard deviation*	*Standard error*
Arterial O_2 saturation at rest (%)	41*	90.4 to 97.0	93.4		
d_{O_2} (volumes %)	35	0.6$_4$ to 1.7$_8$	1.13	±0.36†	
Change in saturation produced by exercise while breathing air (%)‡	26	−2.8 to +4.9	+0.75	±2.36	±0.46
Change in d_{O_2} produced by exercise (volumes %)‡	13	−0.4$_1$ to +1.1$_3$	+0.15	±0.39	±0.11
Arteriovenous O_2 difference (volumes %)	39	2.7 to 6.4	4.6		
Pulmonary capillary flow factor (A)	37	1.2 to 4.7	2.7		

* Arterial oxygen saturation observed only during exercise in remaining three patients.

† The standard deviation of values for d_{O_2} from the average is greater than in this author's original series (±0.25 volumes per 100 cc.) and is presumably attributable to less precise technique among the eleven analysts making these determinations than was attained by the original three analysts.[12]

‡ While the observed direction of change in any individual patient was very likely real, the average response of the group probably represents both variation among patients and variability of a calculation based on four separate gasometric analyses. The average changes in percentage saturation and d_{O_2} are considerably less than twice their standard error and consequently of no statistical significance.

Patients with impaired pulmonary diffusion of oxygen

Data on the 11 patients with impaired pulmonary diffusion of oxygen appear in Table 3. These include seven subjects without right-to-left shunt, three with concomitant right-to-left shunts, and one with the tetralogy of

TABLE 3

OBSERVATIONS ON PATIENTS WITH IMPAIRED PULMONARY DIFFUSION OF OXYGEN

Patient, sex, age and diagnosis	*A-V O_2 diff. (vol. %)*	*Pul. cap. flow factor (Δ)*	*Inspired gas*	*Activity*	*Arterial oxygen*			*Interpretation*	
					Content (vol. %)	*Capacity (vol. %)*	*Sat. (%)*	*l*	*α*
A. Subjects with left-to-right shunts and absence of right-to-left shunt									
1. A.S. ♀ 8 mo.			Air	Crying	9.7	11.4	84	0.16	
Atrial septal defect			100% O_2	Crying	12.2	11.4	100		0
3 mos. later			Air	Crying	9.9	10.8	90	0.10	
			100% O_2	Crying	12.3	11.2	100		0
			Air	Quiet	9.0	9.6	92	0.08	
2. J.E.[a] ♀ 7	4.6	3.1	Air	After exercise	13.5	15.5	86	0.14	
Lutembacher's			Air	Quiet	14.5	15.3	93	0.07	
complex			100% O_2	Quiet	16.3	15.2	100		0
2 years later			100% O_2	After exercise	17.3	16.3	100		0
			Air	Quiet	15.2	16.3	92	0.08	
3. E.W. ♂ 30	6.1	1.6	100% O_2	Quiet	18.9	17.2	100		0
Lutembacher's			Air	Quiet	15.8	17.2	91	0.09	
complex			Air	Exercising	16.0	18.0	88	0.12	
4. E.S. ♀ 6 mo.			Air	Struggling	13.5	15.9	84	0.16	
Ventricular			100% O_2	Struggling	17.2	15.9	100		0
septal defect									

5. D.F.[a] ♂ 14	4.9	1.7	Air	Quiet	15.0	16.5	90	0.10	
Ventricular									
septal defect	6.0	2.1	Air	After exercise	12.2	20.2	60	(0.35)	
			100% O_2	Quiet	20.1	19.2	100		0
			Air	Quiet	16.9	19.3	87	0.13	
22 mos. later			100% O_2	After exercise	17.3	17.3	98		(0.15)
			Air	Quiet	16.0	17.3	91	0.09	
			100% O_2	Quiet	18.3	17.3	100		0
6. T.W.[a] ♂ 16			Air	After exercise	16.8	20.5	81	0.19	
Ventricular			Air	Quiet	18.1	20.0	90	0.10	
septal defect			100% O_2	Quiet	20.8	19.8	100		0
7. J.S.[a] ♂ 4			Air	No record	12.5	13.6	90	0.10	
Patent ductus									
arteriosus			100% O_2	No record	16.0	14.6	100		0
			Air	No record	14.2	15.5	90	0.10	
13 days postop.			Air	No record	14.0	14.7	94	0.06	
			100% O_2	No record	16.1	14.9	100		0
B. Subjects with concomitant left-to-right and right-to-left shunts									
8. S.M. ♀ 17 mo.	4.3*	4.8*	Air	Quiet	16.6†	19.0†	87†	0.13	0.31
Taussig-Bing			Air	Quiet	17.1†	18.8†	90†	0.10	
complex with			Air	Quiet	17.3†	18.8†	91†	0.09	
atrial septal									
defect			Air	Struggling	12.5	19.1	65	(0.23)	
			100% O_2	Struggling	17.4	18.9	91		(0.36)

Patient, sex, age and diagnosis	*A-V O_2 diff. (vol. %)*	*Pul. cap. flow factor (A)*	*Inspired gas*	*Activity*	*Arterial oxygen*			*Interpretation*	
					Content (vol. %)	*Capacity (vol. %)*	*Sat. (%)*	*l*	*a*
9. E.L.[b] ♀ 12	5.2*		Air	Quiet	14.1	17.1	82	0.12	0.19
Large atrial septal defect			100% O_2	Quiet	16.9	17.1	97		
4 mos. later			Air	Quiet	16.9	20.4	82	0.10	0.25
			100% O_2	Quiet	19.7	20.4	95		
10. C.M. ♂ 21	4.8*	0.7	Air	Quiet	23.4	30.6	76	0.11	0.46
Eisenmenger's complex			100% O_2	Quiet	27.5	30.6	89		
C. Patient with large left-to-right shunt produced by Potts-Smith-Gibson aorticopulmonary anastomosis[35]									
11. H.S. ♂ 4	5.0	0.8	100% O_2	Secobarbital	12.7	14.6	86		0.37
Tetralogy of Fallot			100% O_2	Secobarbital	16.3†	15.1†	100†		
6 wks. postop.		2.6	Air	Crying	13.1	16.6	78		
			Air	Quiet	12.9	16.0	80	0.16	0.14
			100% O_2	Quiet	16.2	16.0	99+		
			100% O_2	Crying	16.3	16.0	99+		

Values appearing in parentheses indicate calculations applied to figures obtained during exercise. The arteriovenous oxygen difference observed at rest is assumed in calculating a. Constancy of A-V difference and a is assumed in calculating *l*.

* Value probably representative, but uncertain due to variation among multiple blood oxygen figures, necessitating arbitrary choice of figure for arterial, mixed venous, or pulmonary arteriolar oxygen content.

† Left atrial or pulmonary venous sample.

[a] Previously reported by Ordway, Griffiths, and Nixon.[12]

[b] Previously reported by Ordway.[9]

Fallot in whom an operatively produced left-to-right shunt was a therapeutic measure. The table includes blood oxygen values from which the figures in the last two columns have been calculated.

Systemic blood flow, as inferred from arteriovenous oxygen difference, was within or close to the normal range.

Pulmonary capillary flow was estimated in six patients. It was markedly elevated in three, moderately elevated in two (patients 3 and 5), and markedly reduced in patient 10, who had a concomitant right-to-left shunt. The latter three patients had extremely high pulmonary artery pressures, the highest in this group.* Patient 11 had an abrupt increment of over 300% in pulmonary capillary flow brought about by operative aortico-pulmonary anastomosis.

Impaired pulmonary diffusion of oxygen at rest: six subjects. In patients 5 and 6 the arterial oxygen saturation was 87 to 90% while breathing air, and rose to 100%, with a normal amount of dissolved oxygen, during inhalation of 100% oxygen. In patient 8, 87% saturation of pulmonary capillary blood was observed in a sample removed by catheter from a left pulmonary vein. In patients 9, 10, and 11, all of whom had arterial anoxemia produced by right-to-left shunts, the rise in arterial oxygen saturation produced by breathing oxygen after breathing air was abnormally great, indicating a degree of unsaturation of pulmonary capillary blood expressed by l values of 0.10 to 0.16.

Impaired pulmonary diffusion of oxygen during exercise: eight subjects. In one subject (patient 4) arterial samples were removed only during exercise and showed a rise from 84% while breathing air, to complete saturation, with normal dissolved oxygen, while breathing 100% oxygen.

In three subjects (patients 1, 2, and 3), whose arterial oxygen saturation was normal at rest, exercise produced a fall to levels of 84 to 88%. The anoxemia during exercise was completely overcome in the first two of these during inhalation of 100% oxygen while exercising. The effect of oxygen inhalation during exercise was not determined in patient 3, and consequently it was not demonstrated that his low arterial oxygen saturation while breathing air, 88%, was due to impaired pulmonary diffusion of oxygen and not to reversal of shunt. The latter possibility is unlikely, however, in view of this patient's impediment to free flow of blood in the left side of the heart, afforded by the stenotic mitral valve.

In two patients without right-to-left shunts, the effect of impaired pulmonary diffusion of oxygen, already present at rest, was so greatly enhanced during exercise that cyanosis appeared. In patient 5 the arterial oxygen saturation fell to 60% during inhalation of air, whereas it was 98%

* The relationship between pulmonary arterial pressure and pulmonary capillary flow will be fully discussed in a subsequent report.[11]

during the inhalation of 100% oxygen. The wide difference between these figures indicates marked impairment of pulmonary diffusion of oxygen, expressed by an *l* value of approximately 0.35. The failure to attain complete saturation during inhalation of 100% oxygen demonstrates the appearance during exercise of a small right-to-left shunt, which was not present at rest. The extent of arterial unsaturation produced by this shunt during inhalation of air was, however, quite insignificant in comparison with the marked anoxemia brought about by impaired oxygenation of blood in the lungs. In patient 6 an oximeter attached to the ear made possible continuous observation of the marked arterial anoxemia which appeared during exercise and the breathing of air (Fig. 1).[13] This arterial unsatura-

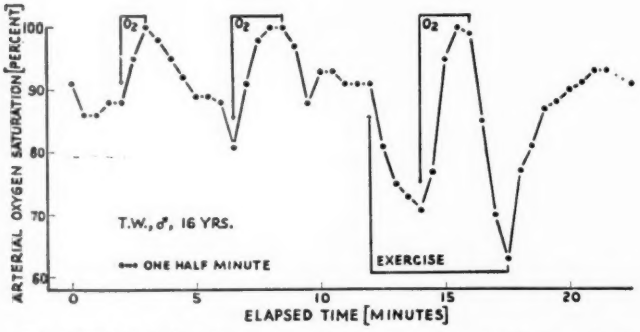


FIG. 1. Patient 6. Ventricular septal defect. Observations with the oximeter at half-minute intervals. Exercise consisted in alternately stepping up onto and down from a step about five inches high. 100% oxygen administered by mask during intervals indicated.

tion was completely overcome by the inhalation of 100% oxygen, showing that it was due to impaired oxygenation in the lungs. Inasmuch as the oximeter does not measure dissolved oxygen, it is not possible to exclude the appearance during exercise of a small, physiologically negligible right-to-left shunt, not present at rest.

In one subject with a right-to-left shunt (patient 8) there was enhancement during exercise of the effect of impaired pulmonary diffusion of oxygen previously demonstrated at rest. There was little change in right-to-left shunt; consequently the low arterial oxygen saturation during inhalation of air reflected an increase in *l* from 0.13 at rest to approximately 0.23 during exercise.

Patient 11 exhibited during exercise change in neither *a* nor *l*.

Change in pulmonary respiratory function with sudden change in pulmonary capillary flow: two subjects. Following ligation of a large patent ductus in patient 7 the arterial oxygen saturation rose within 13 days to

94% from the preoperative level of 90%. The latter, while close to the lower limit of normal, had been observed on two occasions and is believed to illustrate slight unsaturation. This was due in turn to impaired pulmonary diffusion of oxygen, since the arterial oxygen content during the inhalation of 100% oxygen was normal.

Patient 11 became handicapped by the large pulmonary capillary flow produced by his artificial aorticopulmonary shunt. It is assumed that no defect in pulmonary oxygenation existed preoperatively, when his pulmonary capillary flow was low. Six weeks following a threefold augmentation in pulmonary capillary flow, he exhibited considerable impairment of pulmonary diffusion of oxygen. His findings have been discussed in preceding paragraphs.

Discussion

Impaired pulmonary diffusion of oxygen has been demonstrated in a group of subjects to which a large or potentially large left-to-right shunt is a common pathological feature. The mechanism of the impaired pulmonary respiratory function is thus presumably *vascular* in nature. In addition it appears to be *functional* and *reversible,* in view of the observation of prompt appearance of disturbed blood oxygenation when pulmonary capillary flow was suddenly augmented surgically, and its equally prompt disappearance when increased pulmonary capillary flow was suddenly reduced to normal through ligation of a patent ductus. A vascular mechanism which produces respiratory disturbances must operate at the point of contact between the blood and its source of supply of oxygen—namely, at the pulmonary alveolar-capillary membrane.

In the normal person erythrocytes pass through lung capillaries singly. Blood is exposed to the alveolar-capillary membrane for about 0.75 seconds while the subject is at rest and for about 0.34 seconds during muscular exercise.[17] These brief periods of exposure are adequate for the attainment of equilibrium between blood and alveolar air. The amount of blood in the lungs also increases during exercise.[17]

In the individual with a large left-to-right shunt, it is necessary for several times the normal amount of blood to perfuse lung capillaries in the same period of time as a normal amount of blood in the absence of a shunt. This can be accomplished by dilatation of the total pulmonary vascular bed and by a greater linear velocity of blood flow through the capillaries.

All the patients in this study, save a few with small shunts through small defects, showed at fluoroscopy increased lung vascular markings, which in many cases were seen to pulsate. In most subjects this could be correlated with high calculated values for pulmonary capillary flow. In two patients with concomitant left-to-right and right-to-left shunts, in whom pulmonary capillary flow was actually reduced, the roentgenographic and

fluoroscopic appearance of the lung vessels was similar to that in patients with large left- to-right shunts. Very likely these patients did have increased pulmonary capillary flow at a time prior to the present observations, resulting in an increased intrathoracic blood volume and dilated lung vessels which persisted into the phase of reduced pulmonary capillary flow. Vasoconstriction is probably the factor responsible for the reduced pulmonary capillary flow and the associated marked pulmonary arterial hypertension.[23]

The presence of dilated, engorged alveolar capillaries, through which blood flows at an abnormally rapid rate, would constitute a functional barrier to the transfer of oxygen from alveolus to blood stream, if insufficient time should elapse for erythrocytes in the axial part of the stream to become completely equilibrated with alveolar air. Unsaturation of pulmonary capillary blood would result. If now the circulation were speeded up to meet the demands of muscular exercise, the quantity of blood in the lungs might increase, producing even greater capillary dilatation; the period of time spent by each red cell in its transit through alveolar capillaries would be less; the oxygen content of blood entering pulmonary capillaries would be lower due to increased extraction of oxygen by the muscles; and progressive reduction in pulmonary capillary oxygen saturation would ensue. The administration of oxygen in such a situation would promptly overcome the unsaturation of pulmonary capillary blood by effecting a rise in the partial pressure of oxygen in the alveoli. Inasmuch as the alveolus-to-blood oxygen pressure gradient would be expected to remain unchanged, oxygen tension and consequently oxygen content would rise in the pulmonary capillary blood.

Abolition of the pathological condition which has produced the high pulmonary capillary flow, as can be accomplished by ligation or division of a patent ductus, would be expected to be followed promptly by the appearance of normal pulmonary respiratory function.

An anatomical barrier in the form of thickening of the alveolar-capillary membrane could also result in deficient oxygenation of pulmonary capillary blood. Striking arteriolar thickening and sclerosis may occur in the lungs of individuals with large left-to-right shunts,[21] but lesions at this level cannot interfere with gas transfer. Marked changes in the alveolar walls have been described in cases of mitral stenosis,[24] but have never been demonstrated in the lungs of patients with congenital heart disease.

The mechanism of the disturbance in oxygenation of the blood is believed to be illustrated by the lung changes shown in Figure 2. This is a section of lung from a nine-month-old infant, clinically unknown to the author, who died of sepsis arising from a middle ear infection, after a brief, fulminating febrile illness. She was known to have mongolism, had been in Charity Hospital twice before with pneumonia and high fever, and had been observed to be cyanotic. At autopsy she weighed nine pounds and was 64

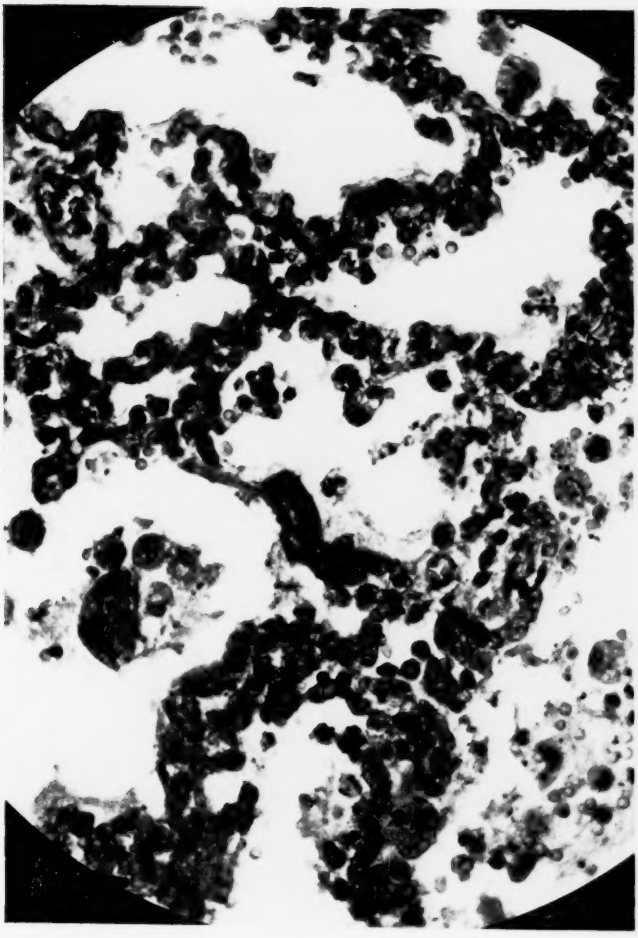


FIG. 2. A.S., female, age nine months. Ventricular septal defect. Photomicrograph of section of lung (description in text).

cm. long. The heart weighed 50 grams and there was marked hypertrophy of the ventricular walls. An oval defect 1.1 cm. in its greatest diameter was present high in the ventricular septum. The lungs were congested but free of edema, and no pneumonia was noted. The microscopic section (Fig. 2) shows thickening of the alveolar walls due to dilated, engorged capillaries, and moderate infiltration of the septa with mononuclear cells and pigment-containing macrophages, some of which lie free in the lumen. There is little evidence of edema.

Certain other mechanisms which might explain the impaired pulmonary diffusion of oxygen exhibited by 11 subjects in this series must be excluded. No patient had clinically recognized signs of pulmonary edema at the time of arterial puncture, although four had presented signs of failure of greater or lesser severity in the preceding month (patients 4, 8, 9, and 11), and one gave a history of failure with pneumonia six months previously (patient 7). Patient 5 gave a history of asthma, but presented no signs of this disorder at the times of examination. In the two subjects with mitral stenosis (patients 2 and 3), the possibility of extensive structural changes in the alveolar walls, as described by Parker and Weiss[14] in this condition, cannot be excluded as the explanation of their impaired pulmonary respiratory function.

Others have described arterial unsaturation and cyanosis in patients with left-to-right shunts, and in several instances the causative rôle of pulmonary factors has been demonstrated or suspected. Koza and Melka[7] in 1929 reported an arterial oxygen saturation of 84.7% in a 24-year-old woman with clinically typical patent ductus arteriosus. They attributed her unsaturation to a right-to-left shunt through the ductus but adduced no substantiating evidence. Chapman and Robbins[4] reported a 37-year-old man with patent ductus arteriosus who experienced a rise in arterial oxygen saturation from 82% while breathing air to 100% while breathing 80% oxygen. The authors recognized that the unsaturation during the inhalation of air was due to pulmonary factors and not a right-to-left shunt, but could not explain the phenomenon on an anatomical basis, since ". . . the alveolar capillaries showed [only] moderate dilatation and some reduplication and tortuosity of their courses . . . [and] . . . the alveolar walls . . . presented only minimal intramural edema and fibrosis." Tucker and Kinney[20] reported a 20-year-old woman with ventricular septal defect who had had cyanosis aggravated by exercise for at least 16 years. "There was clublike dilatation of the intra-alveolar capillaries with marked engorgement and widening of the capillary bed. In other focal areas there were sections of alveolar wall that were avascular and fibrous and thickened to approximately twice the usual width." Brannon, Weens, and Warren[3] described a 39-year-old man with a large atrial septal defect, in whom they demonstrated a left-to-right shunt and a rise in arterial oxygen saturation from 67% while breathing air to 88% while breathing 100% oxygen. This abnormal rise in oxygen

saturation was ascribed to "pulmonary arterial disease" but the concomitant existence of a right-to-left shunt, shown by the arterial unsaturation during oxygen inhalation, was not recognized.*

While all the patients with impaired pulmonary diffusion of oxygen in this series had left-to-right shunts which were large or potentially large, shunts of equal magnitude were observed in patients with normal pulmonary respiratory function. Other, as yet unrecognized factors, therefore, seem to have determined the appearance of this disturbance in any particular individual.

The 18% incidence of impaired pulmonary diffusion of oxygen in persons with left-to-right shunts, observed in this series, is believed to be a conservative estimate of the prevalence of this phenomenon for the following reasons: (i) a few patients with unsaturation of pulmonary capillary blood were not included in the study for want of an acceptable diagnosis; (ii) a few children with left-to-right shunts were not included because arterial unsaturation observed in them while breathing air during general anesthesia could have been due to respiratory depression; and (iii) four children with arterial unsaturation while exercising and breathing air were not included because no observations were made while they were exercising and breathing 100% oxygen.[11]

The arterial unsaturation of the subjects here reported was not in most instances associated with cyanosis. The reasons for this lack of correlation have been well understood since their elucidation by Lundsgaard and Van Slyke in 1923.[6] Within recent years Comroe and Botelho have again called attention to the unreliability of cyanosis as an index of arterial anoxemia.[5]

In view of the facts that a right-to-left shunt may exist without cyanosis, that cyanosis may exist without a right-to-left shunt, and that the intensity of cyanosis is altered by factors (venous unsaturation and concentration of hemoglobin) which do not in themselves produce arterial anoxemia, it appears timely to revise in physiological terms Abbott's clinico-anatomical classification of congenital heart disease,[1] itself a revision of a clinical classification proposed by Bamberger[2] in 1857. The following classification is suggested, based chiefly on observations made possible by the simple procedure of arterial blood oxygen analysis under conditions of inhalation of air and 100% oxygen:

Group 1. No shunt

Group 2. Left-to-right shunt only
- a. Normal pulmonary diffusion of oxygen
- b. Impaired pulmonary diffusion of oxygen

* Case 8 of that report. The anatomical diagnosis was later confirmed at autopsy (personal communication from Dr. Warren). The reported blood oxygen data show l to have been 0.17, a to have been 0.38, and A to have been 1.27. Right ventricular systolic pressure was 112 to 146 mm. Hg.

Group 3. Right-to-left shunt, with or without concomitant left-to-right shunt
- a. Normal pulmonary diffusion of oxygen
- b. Impaired pulmonary diffusion of oxygen

Summary and Conclusions

Impaired pulmonary diffusion of oxygen has been demonstrated in eleven of 62 subjects with left-to-right shunts. In seven of these, without right-to-left shunts, demonstration is based on (i) abnormally low arterial oxygen saturation while breathing air, (ii) rise in saturation to 100% while breathing oxygen, and (iii) a dissolved oxygen content of arterial blood during inhalation of 100% oxygen equal to that in normal persons. In one patient, with a concomitant right-to-left shunt, demonstration is based on an abnormally low oxygen saturation of pulmonary venous blood. In three patients, with concomitant right-to-left shunts, demonstration is based on an abnormally great difference between arterial oxygen saturations observed during the inhalation of air and of 100% oxygen.

The mechanism of impaired pulmonary diffusion of oxygen is believed to be a functional one, related to rapid flow of blood through dilated pulmonary alveolar capillaries in certain individuals who have an augmented pulmonary capillary flow.

A revised classification of congenital heart disease is suggested, based on disturbed physiology rather than clinical appearances.

Acknowledgments

The author gratefully acknowledges contributions of many colleagues in the studies here summarized. Particular thanks go to his professional associates: Drs. S. P. Hendricks, R. L. Bagnetto, A. L. Hyman, R. E. L. Fowler, J. V. Warren, L. F. Nims, and L. Levy, II. The analyses were done by several of the above and by Dorothy Nixon, Peggy Read, Marie Frey, Larry Ashman, Nicholas Nicosia, Adelaide Jacobs, and Frances Vella. Catheterization and arterial puncture were performed on many patients by Drs. H. Jacobs, H. Chastant, H. Strauss, J. Leckert, J. Irion, I. Rosen, S. Brocato, P. Shick, E. Ventre, and R. Romney. Finally, deep appreciation is expressed to Merle Lemieux, who painstakingly recalculated and checked all the figures and was of constant aid in the preparation of the manuscript.

References

1 Abbott, M. E. and Dawson, W. T.: The clinical classification of congenital cardiac disease. With remarks upon its pathological anatomy, diagnosis and treatment. Internat. Clin., Thirty-fourth Series, 1924, *4*, 156.

2 Bamberger, H.: *Lehrbuch der Krankheiten des Herzens.* Vienna, 1857. Cited by Abbott.[1]

3 Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial septal defect. Study of hemodynamics by the technique of right heart catheterization. Am. J. M. Sc., 1945, *210*, 480.

4 Chapman, C. B. and Robbins, S. L.: Patent ductus arteriosus with pulmonary vascular sclerosis and cyanosis. Ann. Int. M., 1944, *21*, 312.

5 Comroe, J. H., Jr., and Botelho, S.: The unreliability of cyanosis in the recognition of arterial anoxemia. Am. J. M. Sc., 1947, *214*, 1.

6 Hyman, A. L., Levy, L., II, Bagnetto, R. L., and Ordway, N. K.: Applications of newer diagnostic methods in congenital heart disease. N. Orleans M. & S. J., 1950, *103,* 5.

7 Koza, F. and Mělka, J.: Nasyceni arterielní krve kyslikem u případu ductus Botalli apertus (Arterial oxygen saturation in cases of patent ductus arteriosus). Bratislavské lekárske listy, 1929, *9,* 842.

8 Lundsgaard, C. and Van Slyke, D. D.: Cyanosis. Medicine, 1923, *2,* 1.

9 Ordway, N. K.: Studies in congenital cardiovascular disease. II. Quantitative evaluation of the factors which produce arterial anoxemia. (Submitted for publication.)

10 Ordway, N. K.: Studies in congenital cardiovascular disease. III. The calculation of left-to-right and mixed shunts. (Submitted for publication.)

11 Ordway, N. K.: Studies in congenital cardiovascular disease. VI. Analysis of the mechanisms involved in the production of late cyanosis. (In preparation.)

12 Ordway, N. K., Griffiths, S. P., and Nixon, D.: Studies in congenital cardiovascular disease. I. Arterial oxygen saturation in left-to-right shunt without right-to-left shunt, during inhalation of air and 100 per cent oxygen. (Submitted for publication.)

13 Ordway, N. K., Warren, J. V., and Nims, L. F.: Observations with the oximeter on the arterial oxygen unsaturation of congenital heart disease. Yale Aeromedical Research Unit Report, No. 58, July 28, 1947.

14 Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path., 1936, *12,* 573.

15 Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of the aorta to a pulmonary artery. Certain types in congenital heart disease. J. Am. M. Ass., 1946, *132,* 627.

16 Preston, S. N. and Ordway, N. K.: Observations of arterial oxygen content in children during the inhalation of air and 100 per cent oxygen. Am. J. Physiol., 1948, *152,* 696.

17 Roughton, F. J. W.: The average time spent by the blood in the human lung capillary and its relation to the rates of CO uptake and elimination in man. Am. J. Physiol., 1945, *143,* 621.

18 Roughton, F. J. W. and Scholander, P. F.: Micro gasometric estimation of the blood gases. I. Oxygen. J. Biol. Chem., 1943, *148,* 541.

19 Taussig, H. B. and Bing, R. J.: Complete transposition of the aorta and a levoposition of the pulmonary artery. Clinical, physiological, and pathological findings. Am. Heart J., 1949, *37,* 551.

20 Tucker, A. W., Jr., and Kinney, T. D.: Interventricular septal defect (Roger's disease) occurring in a mother and her six-month fetus. Am. Heart J., 1945, *30,* 54.

21 Welch, K. J. and Kinney, T. D.: The effect of patent ductus arteriosus and of interauricular and interventricular septal defects on the development of pulmonary vascular lesions. Am. J. Path., 1948, *24,* 729.

TUBERCULOUS MENINGITIS IN CHILDREN*

The Addition of Forty-one Proven Cases
A Critical Analysis of the Literature dealing with Streptomycin Therapy since its Introduction

ROBERT W. SAPPENFIELD,** VERNE G. ROBINSON,†
AND DWAIN N. WALCHER‡¶

In January, 1944, Schatz, Bugie, and Waksman[21] reported the isolation of a new antibacterial substance which was designated as streptomycin. In December, 1944, Feldman and Hinshaw[32] reported their observations on the suppressive effect of streptomycin on the human variety of microbacterium tuberculosis in guinea pigs. In January, 1946, Cooke, Dunphy, and Blake[23] reported in this *Journal* the first human case of tuberculous meningitis treated with streptomycin. At the time the article was published the patient had been observed for four months after therapy had been discontinued. She is still alive six years after the first therapy was given, she has had no relapses, and has received no further streptomycin after the initial 68 days of treatment.[22]

From January 1, 1947, to January 1, 1951, fifty-six patients on whom a clinical diagnosis of tuberculous meningitis was made were seen at this hospital. This diagnosis was bacteriologically proven on thirty-seven patients who were treated, and the series is reported in detail (Table 1). An additional five were proven but died before receiving treatment, and fourteen had strong supporting evidence for the diagnosis of tuberculous meningitis, but the spinal fluid proof could not be obtained.

As the data were analyzed certain observations merited comment, namely, age of the patient, length of illness prior to admission to the hospital, the clinical status of the patient when therapy was started, latent period prior to institution of therapy, and the presence or absence of miliary tuberculosis.

Twenty (54%) of the patients were two years of age or under. Of these, sixteen (80%) were ill for two weeks or more; thirteen (65%) were considered late, i.e., semicomatose or comatose, in the disease when therapy was started; twelve (60%) had miliary tuberculosis. All twenty patients had one or more of these factors complicating their illness; all of these patients died.

---

* Aided by grants from the James Whitcomb Riley Memorial Association.
** Present address: United States Public Health Service, Communicable Disease Center, Epidemic Intelligence Corps, New Orleans.
† Division of Public Health Statistics, Indiana State Board of Health, Indianapolis.
‡ Department of Pediatrics, Indiana University Medical Center, Indianapolis.
¶ Resident in Pediatrics, New Haven Hospital, 1943-1944.
Received for publication December 18, 1951.

When these figures were compared with some observations obtained for the seventeen children over two years of age, a striking contrast was obtained. Eight (47%) were ill for two weeks or more, a difference of 33%; nine (53%) were late in the disease when therapy was started, a difference of 12%; only three (18%) had miliary tuberculosis, a difference of 42% in miliary tuberculosis. The four living patients are in this group.

Lincoln[58] states that prior to streptomycin therapy the longest duration of tuberculous meningitis from the time of onset until death was 63 days, with the average being 19½ days. In a recent review of sixty-six cases Lorber[59] found that the average length of time from the onset of symptoms until the therapy was begun was 14½ days. He pointed out that when a disease has progressed more than two-thirds of the way through its natural course before therapy is started, one is asking a great deal of any therapy, no matter how efficient, to expect a satisfactory outcome.

Though certain investigators feel that the number of days prior to therapy does parallel the clinical status when therapy is begun, a more accurate evaluation can be obtained when one considers both factors. Therefore, both the length of illness and the classification of the clinical status of the patient into early, moderate, and late stages of the disease at the time therapy was initiated has been given. Sixty-five per cent of the patients were ill two weeks or more prior to the institution of therapy. They were ill an average of nineteen days, a striking figure when compared with the average survival of 19½ days without any therapy. Three of the four patients who are living received therapy before the fifteenth day. Four of the patients had one or more relapses. In each instance except one, when the patient was started on therapy prior to two weeks of illness, the patient has survived.

Those patients classified as early were those who had no neurological symptoms, were mainly lethargic, and were completely rational. Only five patients were in this optimal state when therapy was started. Two of these five are living. A third patient in this group survived an initial illness and one relapse, both of which were treated in the early stages, but she died during the second relapse. On the final admission she was late in the disease. The moderate patients were lethargic but not semicomatose and had neurological findings. Ten patients were in this group. They had been ill from four to fifty-two days. It is, therefore, apparent that there is not an absolute correlation between clinical status and the duration of illness. One of these patients has had one relapse returning in the moderate stage of her illness and has survived that episode. One other patient in this group survived for over a year but was critically ill when streptomycin was begun again and died in this relapse. The late patients were semicomatose or comatose. Twenty-two of the thirty-seven patients were late when therapy was begun. They had been ill from ten to sixty days. One of these patients is still under therapy. Another is the son of an itinerant laborer and was re-

TABLE 1

PROVEN CASES OF TUBERCULOUS MENINGITI

No.	Pt.	Adm. date	Age	Illness before therapy	General condition	Family survey	X-ray	Miliary	Skin test	Sugar	Protein	Cells	Smear	Culture	Guinea pig	Streptomycin therapy I.M. gm./day	I.T. mgm
1	JW	1-47	2Y	41	L	Aunt	Mil.	+	+	18	145	80	—	+	0	1	1(
2	SO	3-47	9M	7	E	Father?	Neg.	—	+	24	66	105	+	+	—	1	1(
		7-47	13M	7	E		Neg.	—		28	100	27	—	+	—	1	1(
		2-48	20M	18	L		Neg.	—		18		82	—	—	—	2	
3	BC	6-47	6Y	21	L	Negative	Pulm.	—	+	<15	219	225	+	+	+	2	1(
4	MF	7-47	3½Y	11	E	Mother?	Pulm.	—	+	21	61	144	—	+	—	1	1(
5	JH	8-47	2Y	52	M	G-mother	Mil.	+	—	<15	81	31	—	+	+	1	
6	WL	8-47	7½M	15	L	G-parents	Neg.	+	+	21	90	74	—	+	+	2	1(
7	LD	8-47	6Y	13	L	G-father	Potts Disease	+	—1st	22	180	25	—	+	+	1	
8	SW	10-47	6M	39	M	Mother	Mil.	+	+	32	42	16	+	—	—	2	1
9	PM	11-47	12Y	12	M	Negative	Pulm.	—	—1st	25	110	55	+	+	—	2	1
10	LM	4-48	4½M	15	M	Father	Pulm.	—	+	23	112	13	+	—	+	2	
11	EB	5-48	13M	17	L	Aunt	Pulm.	—	0	715	200	96	+	—	0	2	
12	BG	8-48	13M	19	L	G-father	Mil. Pulm.	+	+	<20	162	92	—	—	+	2	
13	RH	8-48	2Y	35	L	Mother Brother	Pulm.	—	+	23	164	716	+	—	—	2	
14	BV	12-48	11M	27	L	Father	Mil.	+	—1st	31	200	74	+	—	+	1.6	
15	CH	12-48	17M	15	M	Mother? Sister	Mil.	—	0*	<15	122	20	+	—	—	2	
16	KV	12-48	13M	11	M	Father	Mil.	+	+	<15	180	142	+	—	+	2	
17	WP	12-48	18M	4	M	G-father	Mil.			39	105	71	—	—	—	2	
		1-50	3¼Y	15	L		Healed	—	+	<15	138	108	+	+	—	2	
18	ME	1-49	15M	13	L	Uncle	Pulm.	+	+	<15	122	46	—	+	+	2	or
19	LG	2-49	13M	60	L	Father	Neg.	+	+	<15	165	113	+	+	+	2	

TABLE 1†

ENINGITIS AT RILEY HOSPITAL (1947-1950)

reptomycin therapy		*Promi-zole ther-apy*	*Life after ther-apy*	*Outcome*	*Autopsy*	*Comments*
M. /day	I.T. mgm./day					
	100	—	43D	Dead	Not granted	TBC choroiditis
	100	—	120D	Relapse		Patient treated 56 days—did well 2M—then relapsed.
	100	—	186D	Relapse		Treated 145 days—did well 53—then treated 1 day
	9		1D	Dead	Not granted	before death. Total 332 days.
	100	—	8D	Dead	Not granted	
	100	—		Living		
	8	—	87D	Dead	Not granted	Had received 11D streptomycin therapy before admission.
	100	—	2D	Dead	Mil. & TBC meningitis	
		—	2D	Dead	Pulmonary, miliary & TBC meningitis	Died before intrathecal given.
	100	—	120D	Dead	Not granted	
	100	—	108D	Dead	Not granted	
	5	—	75D	Dead	Not granted	Sibling died of TBC meningitis.
	9	—	16D	Dead	Not granted	
	9	—	1D	Dead	Pulmonary, miliary & TBC meningitis	
	10	+	119D	?		Signed out by parents in critical condition.
1.6	8	+	8D	Dead	Not granted	
	8	+	5D	Dead	TBC meningitis and bronchogenic spread in lungs	
	10	+	9D	Dead	Pulmonary, miliary & TBC meningitis	
	25	+	380D	Relapse	TBC meningitis and	Patient treated 141 days—did well 9M then re-exa-
	10	+	101D	Dead	bronchogenic spread in lungs	cerbation—treated—lived 93 days—Total 496 days.
	ordered	—	1D	Dead	Pulmonary, miliary & TBC meningitis	Died before intrathecal medication given.
	10	+	11D	Dead	TBC meningitis, miliary	

No.	Pt.	Adm. date	Age	Illness before therapy	General condition	Family survey	X-ray	Miliary	Skin test	Sugar	Protein	Cells	Smear	Culture	Guinea pig	Streptomycin therapy I.M. gm./day	Streptomycin therapy I.T. mgm./
20	RH	2-49	2⅓Y	12	L	Aunt	Pulm.	+	0	<15	1220	107	+	—	—	1	10
21	MG	2-49	3½Y	10	E	Sister?	Neg.	—	+	<15	64	99	+	+	—	2-4	12
		5-50	4¾Y	8	E		0*			<15	113	119	—	—	—	2	
22	VL	4-49	2Y	10	L	Father	Neg.	—	?1st	<15	81	104	—	+	—	2	
23	KF	5-49	4Y	16	E	Uncle	Pulm.	—	+	<15	120	475	+	+	+	2	17
24	JP	5-49	5Y	13	L	Negative	Pulm.	—	+	<15	64	193	+	+	0	2	18
25	JK	6-49	7Y	12	M	Mother	Neg.	—	+	17	85	700	—	—	+	2	
		3-50	7¾Y	8	M		Neg.	—		27	111	280	+	+	—	2	
26	MM	8-49	8Y	20	L	Negative	Neg.	—	+	<15	64	99	—	+	—	2	
27	MZ	10-49	12Y	12	E	Incomplete	Healed Pulm.	—	+	<15	74	235	+	—	+	2	
28	LH	11-49	13M	11	M	Mother	Mil.	+	+	<15	94	140	+	—	—	2	
29	BW	4-50	3Y	22	L	Incomplete	Pulm.	—	+	<15	50	84	+	+	+	2	
30	JM	5-50	3½Y	47	L	Negative	Neg.	+	+	19	197	210	+	+	+	2	
31	HH	5-50	12Y	16	L	Father	0*	—	—1st	<15	225	318	+	+	+	2	
32	JZ	6-50	10Y	3	E	Negative	Neg.	—	+	40	105	384	+	+	—	2	
33	JD	7-50	20M	40	L	G-mother	Pulm.	—	+	16	850	16	+	—	—	2	
34	BD	7-50	2¼Y	25	L	Negative	Neg.	—	+	<15	58	52	—	+	—	1	
35	JB	8-50	2Y	24	L	Brother	Neg.	—	+	<15	189	86	+	+	+	2	
36	PJ	10-50	21M	17	L	Father?	Neg.	—	+	16	100	3	—	+	+	1	
37	JB	11-50	2½Y	19	L	Mother Father	Neg.	—	+	<15	159	129	+	+	+	2	

* Not done.

† Table 1 was prepared January 1, 1951. Patients reported alive in this table have remained alive and have had

ptomycin herapy I.T. ay mgm./day	Promi-zole ther-apy	Life after ther-apy	Outcome	Autopsy	Comments
10	+	2D	Dead	Pulmonary, miliary & TBC meningitis	
12	+	423D	Relapse		Patient treated 120 days—did well 10½M then relapse—Treated here, then at home 109 days—Total 601 days.
	+	116D	Dead	Not obtained	
	—	4D	Dead	TBC meningitis	Died before intrathecal given.
17	+	40D	Dead	TBC meningitis-pulmonary	
18	+	30D	Dead	Not granted	
	+	276D	Relapse		Treated 59 days—did well 7M then relapsed—Treated 115 days.
		300D	Living		
	+	77D	Dead	Not granted	Had craniotomy.
	+	94D	Dead	Not granted	
	+	49D	Dead	Pulmonary, miliary & TBC meningitis	
	+	10D	Dead	Not granted	
	+	13D	Dead	TBC meningitis-miliary	
	+	35D	Dead	Not granted	
	+	208D	Living		Had clinical diagnosis of TBC meningitis one year before adm. here—treated with streptomycin I.M. and I.T.
	+	15D	Dead	TBC meningitis-pulmonary	Block of spinal canal.
	+	5D	Dead	Not granted	Had pulmonary TBC 14 months previously.
	+	33D	Dead	TBC meningitis	
	+	9D	Dead	Not granted	
	+	43D	Living		Still under therapy.

ave had no relapses as of January 1, 1952.

moved against our advice in a critical condition. All efforts to trace the family and the child have failed. The remainder of this group did not survive.

Since it was observed that an individual can progress to the late stage of the disease within ten days or less, it is of importance to consider the latent period between the time of admission and the institution of therapy. Here, as elsewhere, the indications for the beginning of streptomycin therapy have been altered. Early in the studies it was thought that bacteriological proof must be obtained before streptomycin could be given. Later it was begun after three spinal fluid examinations; now on clinical impression alone streptomycin is started, striving for bacteriological proof later.

In those cases where bacteriological proof is not immediately forthcoming, supporting evidence is derived from the spinal fluid sugar, total protein, and cell count. In tracing the contact history of the children in this series, evidence of active tuberculosis was found in an immediate member of twelve of the families. There was probable tuberculosis in five more families, but they failed to coöperate with subsequent films and examinations to confirm the initial impression. In eleven families an aunt, uncle, or grandparent had tuberculosis; in seven it was impossible to establish a contact history; in two the family survey was admittedly incomplete. There was good evidence that the contact came from an immediate member of the family or close relative in 75% of the cases. The Mantoux was positive in twenty-eight (75%) of the children. One child had a negative tuberculin; two died prior to completing the tuberculin test through the second strength; the record was not complete for the tuberculin reactions on the other six.

In this laboratory both immediate centrifugation of the spinal fluid as well as waiting for pellicle formation is utilized; the spinal fluid is cultured on Lowenstein, Petragnani, and Dubos medium; two spinal fluid samples and two gastric washing samples are routinely inoculated into guinea pigs.

Fifteen (40%) of the patients were clinically diagnosed as having miliary tuberculosis; nine were confirmed at autopsy; another showed residuals of a disseminated process thought to be compatible with the x-ray diagnosis of miliary tuberculosis; one diagnosed as miliary tuberculosis during life was a case of bronchogenic dissemination. In the other four, autopsies were not granted, though one had tuberculous choroiditis. Ten of the fifteen lived less than sixteen days.

From January 1, 1947, through April, 1949, streptomycin was given intramuscularly and intrathecally. The patients received 1 to 2 gms. of streptomycin intramuscularly daily, except for one patient, MG, who received 4 gms. of streptomycin daily in a final desperate attempt to save her life. Therapy was limited to sixty and later 120 days, eventually reaching a point where the clinical condition and the laboratory findings influenced the duration of therapy rather than to have a predetermined length

of time. Intrathecal dosage varied considerably, ranging from 100 mgm. at first to 1 mgm. per kilogram body weight before it was discontinued completely in May, 1949. Intrathecal therapy was given daily unless technical difficulties prevented the installation of streptomycin. Promizole* was started in August, 1948, and usually 2 gms. a day were given. A blood level of 5 mgm. per cent was considered optimum.

We were unable to establish bacteriological proof from the spinal fluid examinations in fourteen patients (Table 2). Support for the clinical diagnosis came from the family history which revealed good contact in eleven cases and probable contact in two more. The chest film was contributory in five cases. The Mantoux was positive in nine cases. Gastric washings were positive in four. Two patients in this group are living today. Tuberculous meningitis was confirmed in the four who came to postmortem examination.

Review of Literature

The discouraging results obtained in the series here prompted a survey of the literature, both in English and in foreign languages. Unfortunately, much of the literature which has been written on this subject since January, 1946, cannot be readily analyzed, for most series still include unproven cases and are not reported in a manner facilitating comparative studies. In doing such an extensive study certain criteria for selection of the cases had to be established and rigidly followed. Only bacteriologically proven cases were included; unfortunately, certain series were invalidated, for the proven cases were mixed with the unproven cases with no possible means of separating them. The only other factor considered in the selection of the cases was the age. Only those cases occurring in children under 16 were included. This age was chosen because the series from here was limited to children. Table 3 lists the cases with as accurate an analysis of each case as the report would permit.

One thousand two hundred and twenty cases were found which met the two criteria. At the time the authors reported their series, 635 were alive, 584 were dead, and the outcome was undetermined from the report of one.

At least 297 had miliary tuberculosis. Inasmuch as the difficulty in establishing the diagnosis of miliary tuberculosis is well known, it is apparent that the statement in regard to the presence of miliary tuberculosis cannot be accepted as proven in all cases. Specific age for 1,029 children was given, with 286 of them being two years or under. From the information given about the patients, either in case histories or from tabulation, 580 could be classified as to their clinical status using the criteria employed earlier in this report; 177 were early in the disease, 235 were moderate, and

* In the early part of this study Promizole was supplied through the courtesy of the Department of Therapeutic Development, Parke, Davis and Company, Detroit.

TABLE 2

UNPROVEN CASES OF TUBERCULOUS MENINGITIS 1947-1950

Pt.	*Age*	*Family survey*	*X-ray*	*Skin test*	*Spinal fluid*			*Gastric*	*Autopsy*	*Comments*
					Cells	*Sugar*	*Bacteriology*			
RA	9M	Sister Mother	Tuberculous Pneumonia	+	13	<15	Negative	Negative	Not granted	Lived 21 days
JB	9Y	?Father	Tuberculous Pneumonia	0	108	<15	Negative	Negative	Pulmonary and tuberculous meningitis	Acid fast bacilli mastoid Lived 13 days
NM	7Y	?Neighbor	Negative	+	260	<15	Negative	Negative		Living
ES	9M	Mother	Pulmonary	0	149	<15	Negative	Positive	Not granted	Lived 30 days
PR	3Y	Mother	Healing Pulmonary	+	4	40	Negative	Negative	Not granted	Lived 45 days
KM	21M	Sister	0	0	18	<15	Negative	0	Pulmonary, miliary and tuberculous meningitis	Lived less than 1 day
DP	11Y	Negative	Negative	+	192	<15	Negative	Negative		First month in another hospital Living
WW	14Y	Sister	Pulmonary Tuberculosis	0	89	34	Negative	Negative	Not granted	Lived 36 days
GS	2Y	Mother	Negative	+	68	22	Negative	Positive	Not granted	Lived 52 days
PE	19M	Sister	Negative	+	30	43	Negative	Negative	Not granted	Lived 40 days
FC	2½Y	Father	Negative	+	34	21	Negative	Positive	Miliary and tuberculous meningitis	Lived 40 days
GB	8M	Mother Brother	Negative	+	27	47	Negative	Positive	Not granted	Lived 33 days
JM	23M	Uncle	Negative	0	35	<15	Negative	Negative	Tuberculous meningitis	Lived 2 days
LL	16M	Mother Sibling	Pneumonia	+	157	<15	Negative	Negative	Not granted	Lived 38 days

TABLE 3

PROVEN CASES OF TUBERCULOUS MENINGITIS IN CHILDREN REPORTED IN THE LITERATURE*

Author	Case No.	Age	Illness before therapy	General condition	Miliary	Streptomycin therapy I.M. gm./day	Streptomycin therapy I.T. mgm./day	Complementary therapy	Life after therapy	Result	Comment
Cooke[22]	1	1Y	8	E	—	0.12-0.24	1-200		6Y+	Alive	
Krafchick[45]	1	15M	9	E	—	0.5 -57D	50-100		150D?	Alive	
Borstein[6]	1	4Y	17+	M	+	1-1.2	100		126D	Dead	Therapy stopped 60D—Restarted 93D
Baggenstoss[3]	1	15M	?	?	+	1 -60D			150D	Dead	Healing of miliary reported
McDermott[58]	1	2Y	?	L	—	1-2 -?	100		75D	Dead	Treated for miliary 10M before
Mursa[63]	1	5Y	8	?	—	0.66 -71D	30	Promin	111D	Alive	
Appelbaum[2]	1	9Y	12	M	+	0.6-1.6 -4M	200		9M	Alive	X-ray clear in 4 months
Nau[64]	1	7Y	23	M	—	0.5 -141D	25-50		1Y	Alive	Left arm weak
Alperin[1]	1	4Y	11+	M	+	1.26 -134D		Promin	364D	Dead	Relapsed 176D—Retreated
	2	18M	3	M	+	1 -87D		Promin	131D	Alive	
	3	9Y	15	M	—	1			51D	Dead	
	4	3Y	5	E	+	1			49D	Alive	X-ray clearing
	8	8Y	36	L	—	1			10D	Dead	
	9	13Y	21	L	—	2			23D	Dead	
Zau[97]	1	6Y	20	EM	—	0.5-1	50-150		52D	Dead	
	5	5Y	21	EM	—	0.5-1	50-150		210D	Alive	
	7	6Y	27	EM	—	0.5-1	50-150		120D	Alive	
	11	4Y	21	L	—	0.5-1	50-150		30D	Alive	
	12	12Y	14	L	—	0.5-1	50-150		18D	Alive	
Stimson[85]	1	10M	10	M	—	1 -116D	100 -75D	Promizole	343D	Dead	Relapsed twice
Tackett[87]	1	13Y	11	M	—	0.8-1.6 -46D	100		774D	Dead	Relapsed twice
Levinson[48, 49]	1	10M	4+	E	+	1.6 -87D	100 -9D		27M	Alive	Relapsed 465D—Treated 73D
	2	12M	10	E	—	1-2 -90D			24M	Alive	Deaf
	3	8Y	3	E	+	1-2 -90D			24M	Alive	
	12	19M	6	E	+	1-2 -90D			98D	Dead	Reported as having relapsed

* The remainder of this table containing data from eighty authors will be included in the reprints.

168 were late. Three hundred and thirty-nine patients were ill less than 15 days prior to the onset of therapy; 168 were ill over 15 days. It was impossible to determine how long 713 had been ill. For 398 cases in the series both the duration of the illness and the clinical condition were given. It is perfectly clear that the two factors are not well correlated, the degree of variability being so great that it would be most unlikely to have the situation altered in a larger group. The standard deviation of the number of days before therapy in each clinical group is so great that considerable overlapping is indicated, even though it is not certain that the distribution is strictly normal.

Since there was great variability in the interval which elapsed from the time the clinician discontinued therapy until he reported his patients, some method of comparative study of the cases had to be devised. Four hundred and thirty-seven children, about whom no essential fact was missing, were classified as early, moderate, and late in their illness. They were then subdivided into various groups—those two years and under; those over two years; those ill 14 days or less; those ill over 14 days; and those with or without miliary tuberculosis. If a patient's condition was last reported at two months, for example, he was then omitted from the statistical calculation at the third month. Therefore, the accompanying graphs indicate the known survivors only for a given month expressed in percentage as determined by dividing the number of known survivors by the number known living plus the number known dead, i.e., the number whose history was completely known (Fig. 1).

In all four graphs those patients two years of age and under have been combined with those over two years. This combination of patients was justified after subjecting each individual group to a statistical study which showed that one was not justified in establishing an arbitrary division of patients at two years and assuming that the prognosis was adversely influenced to a significant degree by the younger age. The method employed in this study was the application of the Chi squared test to a contingency table of monthly survival totals.

The same method was used in the following analysis of the data. Figure 1, Graph A, shows the number of patients reported as surviving at each specific month for a 24-month period. These were the patients who were not reported as having miliary tuberculosis and were started on therapy in less than 15 days from the onset of their illness. This group of patients with the most favorable circumstances was compared with the remaining group, i.e., those who were started on therapy after the second week of illness (those in Graph B) and those who had miliary tuberculosis (those in Graphs C and D). A significantly high Chi squared figure was obtained showing that those in our presumptively most favorable Group A actually did have a better prognosis than the remainder of the series.

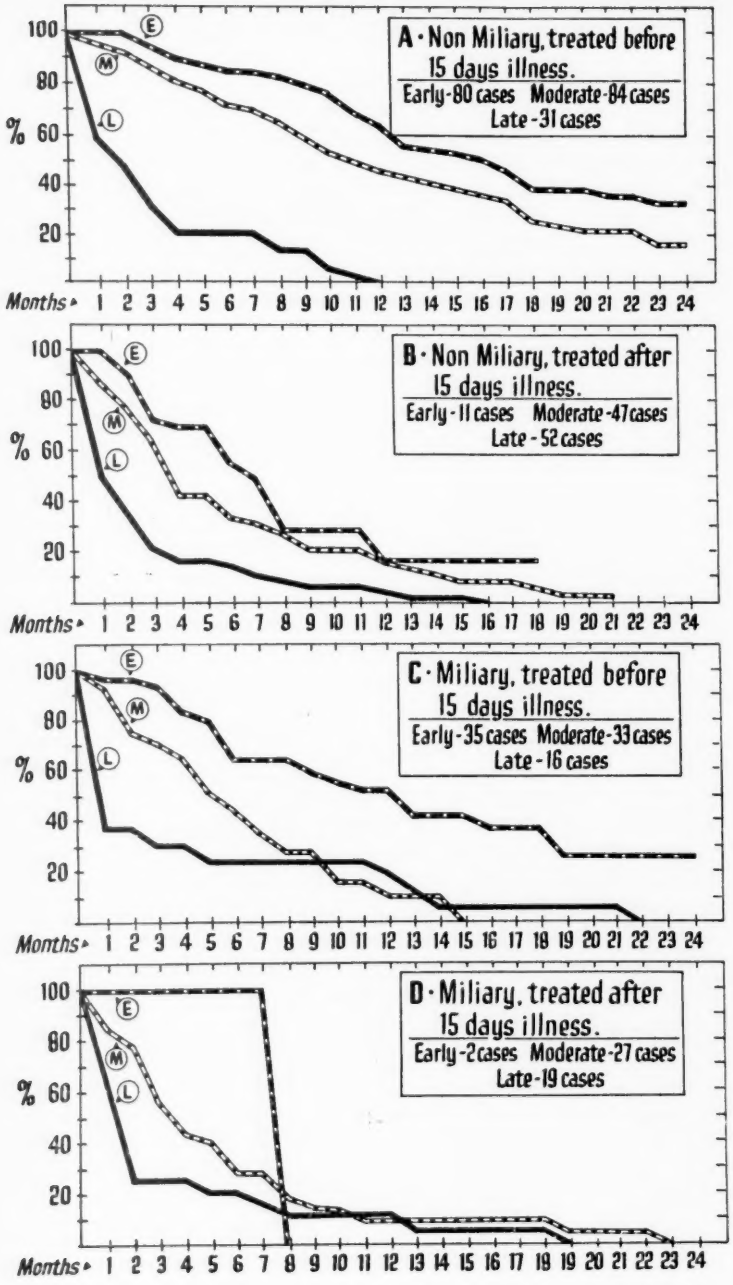

A · Non Miliary, treated before 15 days illness.
Early-80 cases Moderate-84 cases Late-31 cases
B · Non Miliary, treated after 15 days illness.
Early-11 cases Moderate-47 cases Late-52 cases
C · Miliary, treated before 15 days illness.
Early-35 cases Moderate-33 cases Late-16 cases
D · Miliary, treated after 15 days illness.
Early-2 cases Moderate-27 cases Late-19 cases
%
Months
E
M
L

FIG. 1. Percentage of known survivors in the literature with the most complete data.

All those patients with miliary tuberculosis were compared with all those without miliary tuberculosis. It was found that the two groups did not show a significant variation from each other in month-by-month survival. A more minute analysis by clinical condition, i.e., early, moderate, and late stages of the disease, revealed significant differences between the miliary and non-miliary cases in the moderate and late groups, but any difference in the early group could not be proven to be free from chance. The therapy can be grouped into three general categories:

1,220 Patients

IM + IT Streptomycin	IM + IT Streptomycin plus adjunct therapy		Miscellaneous therapy	
657 Patients	521 Patients		42 Patients	
	Promizole	21	IM Streptomycin	29
	Sulphetrone-Streptokinase	34	IM Streptomycin Promin	2
	Promin (Promine)	161	IT Streptomycin	7
	Sulfone	99	Unknown	4
	Tuberculin	159		42
	PPD	12		
	Streptokinase	6		
	PAS	3		
	Sulfone-Dicumerol	1		
	Sulfone or PAS	25		
		521		

The 657 patients who received only intramuscular plus intrathecal streptomycin were compared with the 521 who received intramuscular plus intrathecal streptomycin with some adjunct therapy. Variation in the total dosage and the frequency of administration could not be taken into consideration because of the extreme complexity of the over-all therapeutic regime. It was found that there was no significant difference between the two groups as a whole. However, when those receiving a sulfone were removed from the total number receiving adjunct therapy and then compared with those receiving intramuscular plus intrathecal streptomycin, it was observed that the administration of a sulfone favorably influenced the outcome in the first few months after the administration of the medication. As time progressed, those receiving a sulfone actually faired less well as a group. Those receiving tuberculin which had been given intravenously reversed the pattern, showing a significantly adverse reaction to the tuberculin in the early months, but later on this effect disappeared and those receiving tuberculin did somewhat better after the sixth month. When those receiving intramuscular streptomycin alone were compared with those receiving intramuscular and intrathecal streptomycin without an adjunct, the variation was of no importance.

Discussion

The authors recognize that certain errors in tabulation may have been introduced into this study. A genuine effort was made to obtain all the proven cases of tuberculous meningitis in children recorded in the literature since streptomycin was introduced as a therapeutic agent. It is surely obvious that this effort was unsuccessful to some degree for reasons which are apparent. From the onset of this work it was evident that lack of uniformity in reporting, even as to what might be called a therapeutic success, was to plague us as the various aspects of the over-all problem were analyzed. For this reason the method of the Chi squared test applied to contingency tables of monthly survival totals pervades all the principal calculations.

The history of the development of the present-day therapy for the purulent meningitides is an interesting one. When type specific antisera were first employed, they were introduced intrathecally in a therapeutic gesture. It was observed later that the patient's recovery was not adversely influenced if the serum was not placed directly into the central nervous system, and that actually many of the sequelae attributed to the severity of the disease were being caused by this route of administration, and that if the serum was given intravenously or intramuscularly alone, the patient had a greater opportunity for complete recovery. When the chemotherapeutic and the antibiotic agents were first used, they too were introduced intrathecally.

Actually, it is just recently that most physicians have discontinued the intrathecal administration of penicillin in pneumococcal meningitis, and of streptomycin in Hemophilus influenzae, type b, meningitis. There can be no doubt that this transition has not as yet taken place in the treatment of tuberculous meningitis, for only thirty-one out of the 1,220 patients received intramuscular treatment without intrathecal treatment.

At this hospital the children received intramuscular and intrathecal streptomycin therapy until May, 1949, at which time all intrathecal administration was discontinued. This change in therapy was initiated because data had been accumulating to indicate that significant streptomycin levels were obtained in the spinal fluid from intramuscular streptomycin alone; certain serious complications from the intrathecal injection of streptomycin were being observed, and the rare case given intramuscular streptomycin alone had been reported as doing satisfactorily. Though more of the survivors from this hospital appear in the series receiving intramuscular streptomycin alone, the number is too small to be of significance.

The length of survival of those under two years of age was compared with that observed in those over two years old receiving treatment in this hospital. Those under two had a shorter survival time than those over two. This was attributed to the presence of other adverse circumstances found in the younger children, namely, the greater length of time before the patient

was brought to the hospital for therapy, the more serious clinical condition, and the more frequent presence of miliary tuberculosis. This fact could not be directly compared with the observations made in the literature because those tables had to be established on the percentage of survivals reported.

From the literature it was of no significance to establish an arbitrary dividing point at the age of two years, yet it was possible to show that each individual factor being brought to bear upon the child under two was exerting a deleterious influence. Perhaps inability to prove this difference in response from the literature may be explained by the natural tendency to report therapeutic successes rather than failures; therefore, the figures may be inadvertently weighted.

In both this series and in the literature there was good evidence that the duration of illness inversely influenced the outcome. This would seem obvious. But when the duration of illness was compared with the clinical status, there was little correlation, and it could be shown that the clinical status of the patient at the time of therapy was instituted was of great significance in determining the ultimate outcome.

The presence of miliary tuberculosis adversely influenced the patients seen in this hospital. When the large group was studied, it was surprising to find that the presence of miliary tuberculosis does not influence the outcome if the patient comes to therapy early in the disease, but in the later stages miliary tuberculosis materially alters the outcome. This may be explained by the medication favorably influencing the disseminated disease early in its course, but once it has become well established, medication cannot reverse the process. It should be stated that in the interpretation of the graphs for the influence of miliary tuberculosis on the outcome, the early cases in Graph D were not included because the number of patients was too small.

The beneficial influence of sulfone therapy is interesting in light of the observations of Lincoln[51, 84] on the favorable influence Promizole had upon children with miliary tuberculosis alone. It is tenable that the two drugs, streptomycin and a sulfone, do complement each other to the patient's advantage. It is difficult to explain the apparent late adverse effect of the sulfones on the ratio of the survivors.

The early adverse influence of intravenous tuberculin was not anticipated. One can speculate that the tuberculin served to "light up" the tuberculous process to so great a degree that the patient was unable to handle the additional insult.

Though it could be shown that there was no variation beyond that introduced by chance in the comparison of the survival totals for the patients receiving intramuscular streptomycin alone and those receiving intramuscular plus intrathecal streptomycin, it is impossible to accept this as a valid observation, since the total group receiving intramuscular streptomycin alone was too small.

Summary

Forty-one additional proven cases have been added to the literature. After April, 1949, no patient with tuberculous meningitis at this hospital has received intrathecal medication.

One thousand two hundred and twenty cases of proven tuberculous meningitis in children have been analyzed.

It was possible to demonstrate that those children under two years of age had a poor prognosis from this series, but an arbitrary delineation at the age of two could not be established in those cases taken from the literature. An explanation for this is offered.

The clinical status of the patient is of more value than the duration of illness in estimating the prognosis.

Miliary tuberculosis was shown to influence adversely those who were moderately ill and those who were late in their illness, but it was not possible to demonstrate that it exerted an adverse influence in those treated early.

Sulfones favorably influenced the early outcome of the patients studied in the literature.

Intravenous tuberculin adversely influenced the early outcome of the patients studied in the literature.

References

1 Alperin, L. and Toomey, J. A.: Treatment of tuberculous meningitis. J. Pediat., S. Louis, 1948, *33*, 74.

2 Applebaum, E. and Halkin, C.: Tuberculous meningitis and miliary tuberculosis arrested with streptomycin. J. Am. M. Ass., 1947, *135*, 153.

3 Baggenstoss, A. H., Feldman, W. H., and Hinshaw, H. C.: The effect of streptomycin on the pathology of generalized miliary and meningeal tuberculosis. Proc. Mayo Clin., 1947, *22*, 265.

4 Beguin, M. H.: La streptomycine et le "PAS" dans le traitement de la tuberculose chez l'enfant. Ann. paediat., Basel, Bibliotheca Paediatrica Supplementa, 1949, Fasc. 49, 1-96.

5 Booth, I. S.: Report of case of tuberculous meningitis treated with streptomycin. Med. J. Australia, 1949, *2*, 55.

6 Bornstein, P. K.: Streptomycin in miliary tuberculosis with tuberculous meningitis. Q. Bull. Sea View Hosp., N. Y., 1946, *8*, 219.

7 Boyd, G. L.: Streptomycin in childhood tuberculosis. Canad. M. Ass. J., 1949, *60*, 476.

8 Brainerd, H. D. and Eagle, H. R.: The effect of streptomycin on tuberculous meningitis. Ann. Int. M., 1950, *33*, 397.

9 Brdlík, J. and Houštěk, J.: Výsledky léčby TBC meningitídy po delším časovém odstupu. Pediatrické listy, Prague, 1949, *4*, 179.

10 British Research Council: Streptomycin in the treatment of tuberculous meningitis. Brit. M. J., 1950, *2*, 413.

11 Buding, A. and Schwarze, F.: Erfahrungen mit Streptomycin bei der Meningitis Tuberculosa. Zschr. ges. inn. med., Leipzig, 1949, *4*, 35.

12 Cairns, H. and Taylor, M.: Discussion of streptomycin in meningitis. Proc. R. Soc. M., Lond., 1949, *42*, 155.

13 Cairns, H., Smith, H. V., and Vollum, R. L.: Tuberculous meningitis. J. Am. M. Ass., 1950, *144*, 92.

14 Cathie, I. A. B., and MacFarlane, J. C. W.: Adjuvants to streptomycin in treating tuberculous meningitis in children. Lancet, Lond., 1950, *2*, 784.

15 Cawley, P. F.: Streptomycin in tuberculous meningitis. Brit. M. J., 1950, *1*, 248.

16 Chaptal, J., Brunel, D., and Pietri, J. E.: A propos du traitement de la méningite tuberculeuse de l'enfant par la streptomycine. Présentation de malades. Arch. fr. pédiat., 1949, *6*, 194.

17 Choremis, C., Zervos, N., Constantinides, V., and Pantazis, S.: Streptomycin therapy of tuberculous meningitis in children. Lancet, Lond., 1948, *2*, 595.
18 Choremis, C., Zervos, N., Pantazis, S., Priftis, N., and Papatheodorou, N.: Further observations on the application of streptomycin in the treatment of tuberculous meningitis in the Athens University Pediatric Clinic, covering the period 1-1-48 to 31-12-48. Acta tuberc. scand., 1950, *25*, 8.
19 Cocchi, C.: Therapy of tuberculosis with streptomycin, sulfone, and vitamin A. Riv. clin. pediat., 1948, *46*, 209.
20 Cocchi, C. and Pasquinucci, D. G.: Primi resultati nella terapia delle meningiti tubercolari con la streptomicina associata a solfone e vitamina A. Riv. clin. pediat., 1947, *45*, 193.
21 Cohen, S. and Gans, R. H.: Treatment of tuberculous meningitis with streptomycin. Dis. Chest, 1950, *18*, 215.
22 Cooke, R. E.: Personal communication, June 1951.
23 Cooke, R. E., Dunphy, D. L., and Blake, F. G.: Streptomycin in tuberculous meningitis; A report of its use in a one-year-old infant. Yale J. Biol., 1946, *18*, 221.
24 Debré, R., Brissaud, H. E., Mozziconacci, P., Cousin, M., and Kaplan, A.: Causes des échecs observés dans le traitement de la méningite tuberculeuse de l'enfant par la streptomycine. Arch. fr. pédiat., 1949, *6*, 441.
25 Debré, Robert, Noufflard, H., St. Thieffry, and Brissaud, E.: Streptomycin and tuberculous meningitis in children. Brit. M. J., 1947, *2*, 913.
26 Dolgin, J. and Jaworski, A. A.: Tuberculous meningitis. Q. Bull. Sea View Hosp., N. Y., 1951, *12*, 21.
27 Driessen, O. A.: Twee gevellen van tuberculeuse meningitis. Mschr. kindergeneesk., 1948, *16*, 211.
28 Dubois, R., Linz, R., Delcourt, R., and van Wien, H.: Observations recueillies au cours d'un essai de traitement de la méningite tuberculeuse par la streptomycine. Acta Paediat. Belg., 1949, *3*, 5.
29 Dubois, R., Linz, R., Leschanowski, H., Schlesser, R., and Wattiez, R.: Observations recueillies au cours d'un essai de traitement de la méningite tuberculeuse par la streptomycine. Acta Paediat. Belg., 1946-47, *1*, 195.
30 Erak, P. and Feric, V.: Naša prva iskustva i zapažanja u toku liječenja tuberkuloznog meningitisa sa streptomycinom. Liječ. vjes., 1949, *71*, 91.
31 Erdos, Z.: Zwei mit Streptomycin behandelte Meningitis tuberculosa Fälle. Paediat. danub., Budap., 1948, *3*, 1.
32 Feldman, W. H. and Hinshaw, H. C.: Effects of streptomycin on experimental tuberculosis in guinea pigs. Proc. Mayo Clin., 1944, *19*, 593.
33 Fontan and Verger: Le traitement de la méningitis tuberculeuse de l'enfant par la streptomycine. J. méd. Bordeaux, 1948, *125*, 119.
34 Fouquet, J.: Méningite tuberculeuse de l'enfant et streptomycine: Le diagnostic précoce de la méningite tuberculeuse. Sem. hôp., Paris, 1950, *26*, 844.
35 Frontali, G.: La granulie et la méningite tuberculeuse traitées par la streptomycine (étude de 85 cas). Ann. paediat., Basel, 1948, *171*, 286.
36 Gambarin-Grueff, L. and Grueff, T.: Considerazioni sopra due casi di meningite tubercolare curati con streptominicina, solfone e vit. A. Gazz. med. ital., 1947, *106*, 260.
37 Garcia Alonso, R., Villota, J., Burgoa, L., and Vanaclocha, J.: Meningitis tuberculosa infantil y estreptomicina. Acta pediat., Madr., 1949, *7*, 143.
38 Garsche, R. and Souchon, F.: Zur Klinik der tuberkulösen Meningitis bei Kindern unter prolongierter Streptomyzinbehandlung. Arch. Kinderh., 1950, *138*, 113.
39 Gorter, E.: 13 gevallen van tuberculeuse meningitis behandeld met streptomycine. Mschr. kindergeneesk., Leyden, 1948, *16*, 217.
40 Illanes Benitez, O. and Blanco, M. Latorre: Tratamiento de la meningitis tuberculosa con estreptomecina (communicación preliminar.). Rev. chilena pediat., 1947, *18*, 390.
41 Illingworth, R. S.: The early diagnosis of tuberculous meningitis. Brit. M. J., 1950, *1*, 479.
42 Jamieson, W. M.: Some problems in the diagnosis of meningeal tuberculosis. Edinburgh M. J., 1949, *56*, 221.
43 Jurow: Tuberculous meningitis. Arch. Pediat., N. Y., 1950, *67*, 238.
44 Klepacki, W.: Results of treatment of tuberculosis with streptomycin. Polski tygod. lek., 1949, *4*.
45 Krafchik, L. L.: Tuberculous meningitis treated with streptomycin. J. Am. M. Ass., 1946, *132*, 375.

46 Lapin, J. H.: Successful medical treatment of obstructive hydrocephalus in tuberculous meningitis. N. York State J. M., 1950, *50*, 1615.
47 Lesńe, E., Cayla, A., Roche, G., and Allard: Tuberculose congénitale transplacentaire avec méningite guérie par la streptomycine. Sem. hôp. Paris, 1949, *25*, 2803.
48 Levinson, A.: Streptomycin therapy in tuberculous meningitis. Am. J. Dis. Child., 1949, *77*, 709.
49 Levinson, A.: Further studies on streptomycin in tuberculous meningitis. Q. Bull. Northwest. Univ. M. School, 1949, *23*, 305.
50 Lincoln, E. M.: Tuberculous meningitis in children, with special reference to serous meningitis; tuberculous meningitis. Am. Rev. Tuberc., 1947, *56*, 75-94; 95-109.
51 Lincoln, E. M. and Kirmse, T. W.: Chemotherapy of tuberculosis in children. Pediatrics, 1950, *5*, 280.
52 Lincoln, E. M. and Kirmse, T. W.: Streptomycin and promizole in miliary tuberculosis and tuberculous meningitis in children. Lancet, Lond., 1949, *1*, 767.
53 Lincoln, E. M. and Kirmse, T. W.: The diagnosis and treatment of tuberculous meningitis in children. Am. J. M. Sc., 1950, *219*, 382.
54 Lincoln, E. M., Stone, S., and Hoffman, O. R.: The treatment of miliary tuberculosis with promizole. Bull. Johns Hopkins Hosp., 1948, *82*, 56.
55 Loeschke, A.: Zur Kritik der Streptomycinanwedung bei der Meningitis tuberculosa. Arch. Kinderh., 1948, *135*, 159.
56 Lorber, J.: The delay in the diagnosis of tuberculous meningitis and its relation to the results of treatment. Proc. R. Soc. M., Lond., 1951, *44*, 1.
57 MacCarthy, D. and Mann, T. P.: Tuberculous meningitis in children, rhythm of treatment, prognosis and results. Lancet, Lond., 1950, *1*, 341.
58 McDermott, W., Muschenheim, C., Hadley, S., Bunn, P. A., and Gorman, R. V.: Streptomycin in the treatment of tuberculosis in humans. I. Meningitis and generalized hematogenous tuberculosis. Ann. Int. M., 1947, *27*, 769.
59 McSweeney, C. J.: The treatment of tuberculous meningitis. Tubercle, Lond., 1950, *31*, 210.
60 Medical Research Council: Streptomycin treatment of tuberculous meningitis. Lancet, Lond., 1948, *1*, 582.
61 Minkenhof, J. E., Sangster, E., Wessel, C., and Bacchini-zwaagdijk, T. E.: Streptomycin therapy of tuberculous meningitis; 4 cases. Mschr. kindergeneesk., 1948, *16*, 192.
62 Mouriquand, G., Dechavanne, D., Fayard, C., and Ruesch, F.: Granulies, méningites tuberculeuses et streptomycine. Pédiatrie, Paris, 1950, *39*, 140.
63 Mursa, M., Reis, J., and Woiski, J. R.: Treatment of tuberculous meningitis with streptomycin. J. Am. M. Ass., 1947, *134*, 1196.
64 Nau, O. S. and Wenzler, F. J.: Tuberculous meningitis treated with streptomycin. J. Pediat., S. Louis, 1948, *32*, 410.
65 Ogura, G. I. and Denst, J.: The effect of streptomycin on the lesions of tuberculous meningitis. Dis. Chest, 1950, *18*, 291.
66 Orrego Puelma, H.: Tratamiento de la meningitis tuberculosa con streptomycina. Ap. resp. & tuberc., Santiago, 1948, *13*, 227.
67 Pasquinucci, D. G.: Considerazioni sulla statistica di 183 casi di meningite TBC. ammessi nella clinica pediatrica di firenze dall' 11-12-1946 al 30-6-1948 e trattati con streptomicina, sulfone e vitamina A. Riv. clin. pediat., 1949, *47*, 6.
68 Peluffo, E.: Cuatro casos de meningitis tuberculosa en niños tratados con estreptomicina. Arch. pediat. Uruguay, 1948, *19*, 357.
69 Quaiser, K.: Erfahrungen mit streptomycin bei meningitis tuberculosa. Oesterreichische Zschr. Kinderh., 1950, *4*, 280.
70 Ramon Guerra, A., Salgado Lanza, A., Scolpini, V., and Prunell, A.: Meningitis estreptomicinica y meningitis tuberculosa. Arch. pediat., Uruguay, 1949, *20*, 276.
71 Ricci, G.: Sulla condotta terapeutica della meningite tubercolare con streptomicina. Importanza essenziale della "cura precoce." Pediatria (Arch.) Nap., 1948, *56*, 211.
72 Rich, C. B. and Samuels, A. J.: Tuberculous meningitis treated with streptomycin. Canad. M. Ass. J., 1948, *58*, 282.
73 Rigdon, R. H. and Lefeber, E. J.: Thrombosis of cerebral vessels with necrosis of the basal nuclei; complication of tuberculous meningitis and streptomycin therapy. Am. Rev. Tuberc., 1950, *61*, 247.

74 Rivoire, R. and Rauch, A.: Streptomycine et méningites. Pédiatrie, Lyons, 1950, *5*, 151.
75 Romero Escacena, G., Barnuevo, L. Y., and Bolinches, J.: Meningitis tuberculosa curada con estreptomicina. Rev. clín. españ., 1948, *29*, 246.
76 Ross, J. D.: Streptomycin treatment of meningeal, miliary and pulmonary tuberculosis. Edinburgh M. J., 1949, *56*, 1.
77 Rossi, E. and Perabo, F.: El tratamiento actual de la meningitis tuberculosa y los resultados obtenidos en el Kinderspital de Zurich. Acta pediat., Madr., 1950, *8*, 407.
78 Rossi, E.: Der Heutige stand der therapie der tuberkulosen meningitiden und ihre ergebrisse im Kinderspital Zurich. Helvet. paediat. acta, 1950, *5*, 27.
79 Rubie, J. and Mohun, A. F.: Tuberculous meningitis—early diagnosis and a review of treatment with streptomycin. Brit. M. J., 1949, *1*, 338.
80 Russell, S. J. M. and MacArthur P.: Treatment of tuberculous meningitis with streptomycin. Lancet, Lond., 1950, *1*, 59.
81 Schatz, A., Bugie, E., and Waksman, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram positive and gram negative bacteria. Proc. Soc. Exp. Biol., N. Y., 1944, *55*, 66.
82 Sims, E. B.: A case of tuberculous meningitis treated with streptomycin without success. Med. J. Australia, 1947, *2*, 12.
83 Smith, H.: Personal communication.
84 Smith, H.: Tuberculous meningitis. Lancet, Lond., 1948, *1*, 379.
85 Stimson, P. M.: Tuberculous meningitis; pulmonary tuberculosis. Arch. Pediat., N. Y., 1949, *66*, 82.
86 Su, T. F. and Wu, M. Y.: Streptomycin and promizole combined therapy in tuberculous meningitis in children. J. Pediat., S. Louis, 1950, *36*, 295.
87 Tackett, H. S. and Lovejoy, G. S.: Prolonged survival following streptomycin therapy of tuberculous meningitis. J. Am. M. Ass., 1950, *142*, 648.
88 Todorovic, K., Milosevic, M., Nikolic, M., and Sovrlic, D.: Présentation de 10 malades survivants et améliorés atteints de meningite tuberculeuse traités par la streptomycine. Arch. Serbes de Medćine, Belgrade, 1949, *47*, 742.
89 van Creveld, S. and Stoppelman, M. R. H.: Streptomycin therapy of tuberculous meningitis of children. Mschr. kindergeneesk., 1949, *17*, 77.
90 van Lookeren Campagne, J.: Uitkomsten van de behandling van meningitis tuberculosa met streptomycine in de graningse Kinderkliniek in 1947. Mschr. kindergeneesk., 1948, *16*, 237.
91 van Zeben, W.: Streptomycin therapy of meningitis. Mschr. kindergeneesk., 1948, *16*, 176.
92 van Zeben, W. and Willemijns, F. A.: Streptomycin therapy of tuberculous meningitis in children's clinic of University of Utrecht; 2 cases. Mschr. kindergeneesk., 1948, *16*, 184.
93 Vassilevitch, N. O.: Therapeutic use of streptomycin in tuberculous meningitis in children. Probl. tuberk., Moskva, 1948, *5*, 22.
94 Vogt, A.: Le traitement de la méningite tuberculeuse de l'enfant par la streptomycine. Rev. méd. Suisse rom., 1948, *68*, 113.
95 Wissler, H. and Streit, M.: Zur Streptomycinbehandlung der Meningitis tuberculosa. Praxis, Bern, 1947, *36*, 445.
96 Wright, G. P. and Rees, R. J. W.: Brains from streptomycin-treated cases of tuberculous meningitis. Proc. R. Soc. M., Lond., 1948, *41*, 456.
97 Zau, F. D. and Wong, Y. T.: Streptomycin in tuberculous meningitis. Chinese M. J., 1948, *66*, 544.

PASSIVE IMMUNITY TO VACCINIA IN NEWBORNS

I. Placental Transmission of Antibodies*

C. HENRY KEMPE**

A hemagglutination-inhibition test for the determination of vaccinia antibodies in serum was first described by Nagler.[6] It has been used extensively by us in a standardized form.[2] Collier[3] has utilized a modification of the method in his study of adults. The present report deals with the determination of the titre of vaccinia antibodies in the sera of 182 mothers at term and in the cord blood of their newborn offsprings. Of the mothers, 102 had been vaccinated within the past five years, while 80 had been vaccinated more than five years ago.

Methods

A standardized procedure of determining vaccinia hemagglutination-inhibition antibodies in serum has been described previously.[2] A suspension of vaccinia-infected allantoic membranes is used as the antigen. Fowl cells susceptible to hemagglutination with the vaccinia-variola group of viruses are utilized in a concentration of 0.5 per cent in Alsever's solution. A single hemagglutinating unit is defined as that dilution of the antigen which produces definite hemagglutination of 0.25 cc. of a 0.5 per cent suspension of vaccinia-sensitive fowl cells. The specificity of this reaction is shown as follows:

(i) Serum of vaccinated individuals inhibits this agglutination to a reproducible titre.

(ii) There is failure of inhibition of agglutination by sera of non-immune rabbits.

Sera for antibody determination are diluted in 10 Kahn tubes in two-fold dilution in 0.85 per cent saline solution (1:5 to 1:2560). The volume of diluted serum is 0.25 ml. To the serum dilutions, 0.25 ml. of antigen dilution containing two hemagglutinating units is added. Known positive and negative control sera are included. An antigen control is set up in which the antigen dilution used in the test is diluted in saline. Racks are shaken and incubated for one hour at 35° to 37° C. Then 0.25 ml. of 0.5 per cent fowl cell suspension is added, the racks shaken and allowed to stand at room temperature until the cells are settled. After one hour, the pattern of sedimented cells is examined. The greatest serum dilution which produces complete inhibition of agglutination is recorded as the hemagglutination-inhibition titre of that serum. The tube containing this dilution should present the same pattern as a control tube with 0.25 ml. of vaccinia-sensitive red cell suspension and 0.5 ml. of saline. The negative control

---

* From the Division of Pediatrics, University of California School of Medicine, and the George Williams Hooper Foundation, San Francisco, California. This study was supported in part by the E. Charles Fleischner Fund for the Study and Prevention of Communicable Diseases in Childhood and by the Research Committee of the University of California School of Medicine.

** Assistant Resident in Pediatrics, New Haven Hospital, 1948-1949.

Acknowledgment is made for the technical assistance of J. Richard Jackson, and the co-operation of A. S. Benenson, M. C. USA, Francis Scott Smyth, M.D., Edward B. Shaw, M.D., and Henry K. Silver, M.D.

Received for publication December 1, 1951.

serum should show no inhibition of agglutination, while the positive control should show inhibition within one dilution of its usual titre. Complement fixation tests also were performed on 141 of the sera using two units of soluble vaccinia antigen, two units of complement, with fixation for 2½ hours at 37° C.

Results

Serologic studies were performed on 182 mothers at term and on cord bloods of their 182 newborn infants. Figure 1 shows the hemagglutination-inhibition titers of these sera. For purposes of analysis these individuals were placed in one of four groups:

(i) 102 mothers vaccinated within the past five years;
(ii) their 102 newborn infants;
(iii) 80 mothers vaccinated more than five years ago;
(iv) their 80 newborn infants.

The data are plotted in terms of per cent of individuals with titres less than any chosen level.

Figure 1 shows that only 20 per cent of the mothers vaccinated within the past five years had hemagglutination-inhibition titres greater than 1:80, while 48 per cent of their newborn infants had titres above that level. Only 14 per cent of the mothers vaccinated more than five years ago had titres

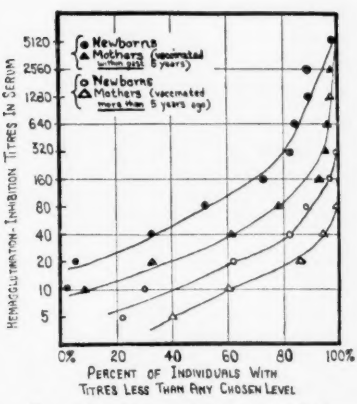


Fig. 1. Hemagglutination-inhibition titres in serum of 182 mothers at term and on cord bloods of their newborn infants.

As a group, infants have consistently higher antibody titres than their mothers. Mothers vaccinated within five years have titres higher than those vaccinated earlier, as do their respective groups of infants.

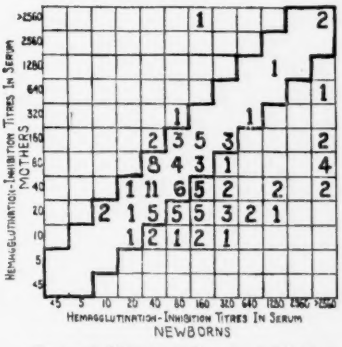


Chart 1. Hemagglutination-inhibition titres in serum of 102 mothers (vaccinated within five years) and their newborn infants.

Figures represent the number of instances in which the mother's titre and that of her newborn infant were found at the levels indicated. All numbers within the blocked area represent instances in which the mother's titre was found to be identical to that of her infant. Numbers to the right of the blocked area indicate instances in which the infants' titres were significantly higher than their mothers'.

greater than 1:20, while 38 per cent of their newborn infants had titres above this level.

Chart 1 and Chart 2 give the number of instances in which the mother's titer is present at a given level, when plotted against the titer of the serum of her newborn infant. Chart 1 refers to the mothers vaccinated within five years and their newborn infants; Chart 2 refers to the mothers vaccinated more than five years ago and their infants. The area enclosed by the heavy lines includes the instances where the titres of the mothers' serum and of

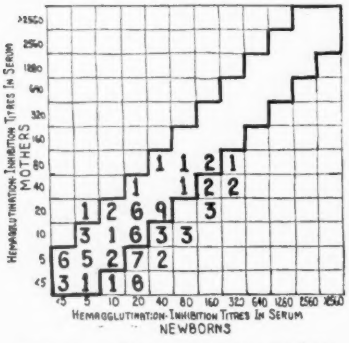


CHART 2. Hemagglutination-inhibition titres in serum of 80 mothers (vaccinated over five years ago) and their newborn infants.

Figures represent the number of instances in which the mother's titre and that of her newborn infant were found at the levels indicated. All numbers within the blocked area represent instances in which the mother's titre was found to be identical to that of her infant. Numbers to the right of the blocked area indicate instances in which the infants' titres were significantly higher than their mothers'.

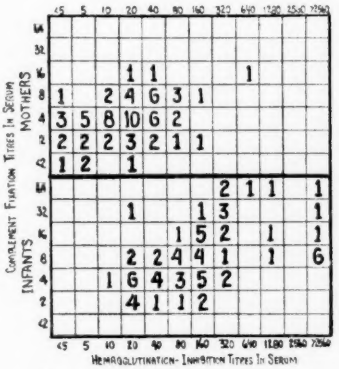


CHART 3. Complement-fixation titres in the serum of mothers and their infants in 141 instances in which the infants had shown higher hemagglutination-inhibition titres than their mothers.

The complement-fixation titres of these infants is also significantly higher than those of their mothers.

their newborns are identical or differ by one dilution in either direction—the latter differences being considered to be within the error of the test.

In the group shown in Chart 1, 41 out of 102 of the newborn infants have titres significantly higher than their mothers, while only four of the 102 are significantly lower. The results shown in Chart 2 indicate that 30 out of 80 have titres significantly higher than their mothers, while only one of the 80 is significantly lower.

In order to test whether these higher titres, in fact, represent specific antivaccinia substance, complement-fixation tests also were performed on the sera of 141 of the infants and their mothers. Chart 3 shows that, in general, newborn infants who have hemagglutination-inhibition titres higher than their mothers also show higher complement-fixation titres. Fairly good

correlation between these two very distinct antibodies is apparent, indicating presence of a specific immune substance.

Discussion

The findings of consistently higher antibody titres in the blood of newborn infants, when compared to their own mothers, are of great interest and are not readily explained. They suggest that actual immune substance is being measured and this tends to be borne out by the preliminary experiments subsequently described. The higher concentration may be explained on the basis of concentration in the placenta and corresponding diaplacental transfer. This has been discussed by Doerr.[4] Such passively transferred and, perhaps, enhanced immunity immediately following smallpox vaccination of the mother may have definite clinical significance in pediatrics.

Summary

1. A comparison of the hemagglutination-inhibition titres of 182 mothers at term and their newborn infants reveal consistently higher titres in the infants in a significant number of cases.

2. Mothers vaccinated within the past five years have higher titres than those vaccinated earlier.

3. Infants of mothers vaccinated within the past five years have significantly higher titres than those whose mothers were vaccinated more than five years ago.

II. Response to Vaccinations

A preliminary attempt to evaluate the significance of occasional high levels of hemagglutination-inhibition antibody titres in cord blood was made. Four newborn infants were vaccinated on the fifth day of life. Two of these had had very high titres in the serum, while the other two had had very low titres. The two infants (A.R. and B.D.) with high antibody titres failed to show any skin reactions at the site of vaccination, despite three attempts at vaccination. The two (R.W. and C.O.) with low antibody titres had a "vaccinia-take," with maximum skin reaction occurring on the tenth day after the vaccination. Figure 2 shows the serologic response of these four infants.

At approximately six months of age, repeat vaccinations were performed on three of the four infants. Prior to revaccination infant A.R. had a residual antibody titre of 1:40, while B.D. had a titre of 1:160, and infant C.O. had a titre of 1:10. Revaccination of these three infants produced no allergic or immune early response in patients A.R. and B.D., and resulted in an early sensitivity response in infant C.O. followed by a typical vaccinoid reaction, maximal on the sixth day.

Infants A.R. and B.D. developed a reaction maximal on the fifth and sixth days, respectively. Had it not been for the absence of an early sensi-

tivity type of reaction, indicating a lack of previous antigenic experience to the virus, these reactions would undoubtedly be called vaccinoid. However, in the absence of this type of sensitivity reaction and the known findings of a high titre of passively acquired antibodies, it is suggested that these were modified primary "vaccinia takes." A third vaccination performed on these two children (A.R. and B.D.), at the age of one year, resulted in a sensitivity type or immune early reaction maximal on the second day after vaccination.

Discussion

Failure to react in any way to vaccination has in the past invariably been ascribed to faulty technique or the use of inactive inoculant. Over the years,

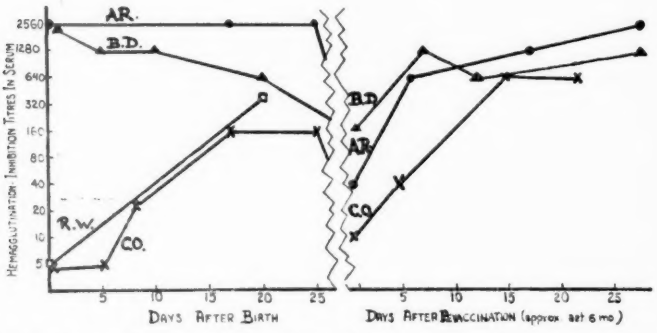


Fig. 2. Hemagglutination-inhibition titres of four newborn infants at time of birth and following vaccination at five days of age.

Three of these infants were revaccinated at around six months of age and their antibody response shown.

however, pediatricians have pointed to instances where children did not respond to vaccination with material known to be highly active in other cases. The observations on two infants herein reported suggest that, at least early in life, passively acquired immunity might, in fact, interfere with dermal infection to live vaccinia virus and result in a true "no take." The immediate reaction, reaching its maximum within 72 hours after vaccination, is an allergic reaction to vaccinia antigens. It denotes previous antigenic experience, usually through successful vaccination.[1, 6, 7] This reaction is not seen in unvaccinated infants but is present virtually in all revaccinated children.

In the absence of an early sensitivity response suggestive of previous antigenic experience, accelerated vaccinia resembling a vaccinoid reaction may represent modification of the infection by passively acquired immunity present in the tissue.

Summary

1. Two newborn infants with high hemagglutination-inhibition antibody titres in their sera could not be successfully vaccinated in the first two weeks of life and these may represent instances of actual "no takes."

2. Two newborn infants with low hemagglutination-inhibition antibody titres in their sera were successfully vaccinated in the first week of life and demonstrated a rise in antibody titre.

3. At the age of six months repeat vaccination of the two infants with high titres resulted in a skin reaction maximal on the fifth and sixth days, respectively, in the absence of an earlier sensitivity type of reaction. This suggests that no previous antigenic experience had occurred and that the present response was, in fact, a modified vaccinia or accelerated primary response. Serologic data on these patients have been presented.

References

1 Benenson, A. S.: Immediate (so-called "immune") reaction to smallpox vaccination. J. Am. M. Ass., 1950, *143*, 1238.

2 Benenson, A. S. and Kempe, C. Henry: Immunologic response to vaccination with inactivated cowpox vaccine. Fed. Proc., Balt., 1951, *10*, 402.

3 Collier, W. A.: Individual immunity against smallpox. Doc. neerl. indon. Morb., trop., 1951, *3*, 163.

4 Doerr, R.: Zur permeabilitat der Plazenta. Schweiz. med. Wschr., 1941, *22*, 1253.

5 Nagler, F. P. O.: Application of Hirst's phenomenon to the titration of vaccinia virus and vaccinia immune serum. Med. J. Australia, 1942, *1*, 281.

6 Von Pirquet, C. E.: Allergy. Arch. Int. M., 1911, *7*, 259; 383.

7 Von Pirquet, C. E.: Die Doppelreaktion dei der Kyhpockenimpfung. Münch. med. Wschr., 1911, *58*, 937.

THE BEHAVIOURAL RESPONSE OF INFANTS TO HEAT STRESS*

ROBERT E. COOKE**†

The influence of environmental temperature on the water and electrolyte balance of infants has been studied by Cooke, Pratt, and Darrow and reported in this journal.[8] However, changes in the feeding behaviour and activity of infants exposed to heat stress have not been extensively studied.

The suppression of food intake in adults by high environmental temperature has been known for years,[10] but the influence of psychic factors in adults complicates these results. In the laboratory the relationship between food and water intake and environmental temperature has been studied in several species[2, 11, 12, 16] with fairly consistent lowering of the food intake with heat stress.

The human infant is in many ways comparable to the laboratory animal in being relatively free of habit and prejudice. Therefore, a study of the feeding behaviour of infants may be of value in understanding the physiological mechanisms underlying the regulation of food intake in the human species.

It is the purpose of this paper to report the influence of environmental temperature on the food and water intake of human infants. A few other somewhat unrelated effects of environmental temperature on their behaviour will be mentioned.

METHODS

Six normal infants ranging in age from 14 to 231 days were studied with no clothing except diapers in a room of accurately controlled temperature, sound, and lighting for periods of 20 to 180 days. The same nursing personnel were constantly in attendance throughout the whole study. These nurses were motherly people and provided a fairly satisfactory emotional environment for the babies. No more than two infants were studied simultaneously so that ample time was available for individual play and feeding.

A program for complete ad libitum feeding of young infants both with respect to time and volume of feeding was modelled after that described by C. M. Davis[5] and others.[13, 17] This program consisted of feeding the infant whenever hungry and offering as much as would be taken without urging. The criteria for deciding that an infant was hungry were active crying, not abolished by holding, changing of diapers, etc., active sucking movements, and/or extreme restlessness and activity.

---

* From the Metabolic Study Unit of the Department of Pediatrics, Yale University School of Medicine. This work was aided by research grants from the United States Public Health Service and the James Hudson Brown Memorial Fund.

** Resident in Pediatrics, New Haven Hospital, 1950-1951.

† This work was carried out during the tenure of a National Institute of Health Postdoctorate Fellowship.

Received for publication December 1, 1951.

At each feeding, boiled water was offered prior to the milk mixture. The infant was allowed to drink as much water as desired until the nipple was repeatedly rejected and then a milk mixture was substituted. Then the baby was allowed to drink as much milk as desired until the nipple was again consistently rejected.

Bottles of water and milk mixture were accurately weighed before and after each feeding and the intake of each was determined by difference. The total intake was thereby calculated for each 24-hour period. The feeding mixture consisted of the usual proportions of evaporated milk, sugar and water supplemented by adequate amounts of a water-miscible multivitamin preparation. The caloric density of the milk mixture was 0.80 Calorie per cc.

The environmental temperature was kept at 81° ± 1° F. during the control periods and at 91° ± 1° F. during the hot periods. The relative humidity ranged from 40 to 50 per cent.

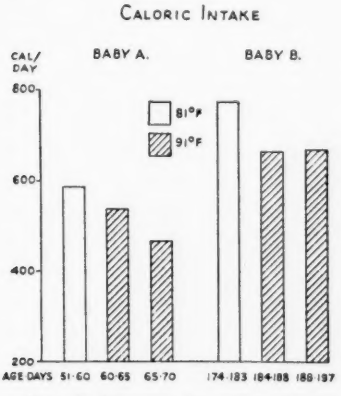


FIG. 1. Decrease in caloric intake with rise in environmental temperature.

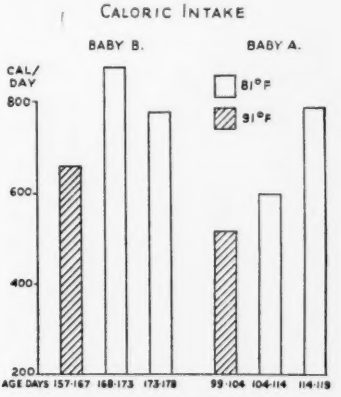


FIG. 2. Increase in caloric intake with fall in environmental temperature.

RESULTS

Food intake. At 81° F. the caloric intake of these infants fed strictly ad libitum as regards time, frequency, and quantity of feeding was remarkably close to the accepted optimal caloric intake. The intakes for these infants for approximately 35 periods of study ranged from 90 to 154 Calories per kilogram of body weight per day and averaged 120 Calories.

To demonstrate the effect of environmental temperature, the average food intake for a 10-day period preceding a change in environmental temperature was compared with the average intake for the period (4-7 days) immediately following this change and also for a period several days (10-15) thereafter. In general there was a consistent fall in caloric intake when the environmental temperature was raised from 81° to 91° F. (Fig. 1), the intake averaging 105 Calories per kilogram per day. Conversely, there was a rise in caloric intake accompanying the lowering of room temperature from 91° to 81° F. (Fig. 2). These changes were considerably less in the

younger infant and in the course of three months the response in the same child became considerably greater (Fig. 3).

Water intake. At 81° F., the intake of boiled water as distinct from the water of the milk mixture was relatively small, ranging from 14 to 302 cc. per day and averaging 97 cc. per day.

The intake of distilled water increased markedly with a rise in environmental temperature (Fig. 4); it ranged from 32 to 347 cc. per day and averaged 168 cc. Likewise, the fall in water intake with a fall in room temperature was striking (Fig. 5). As with caloric intake, the changes

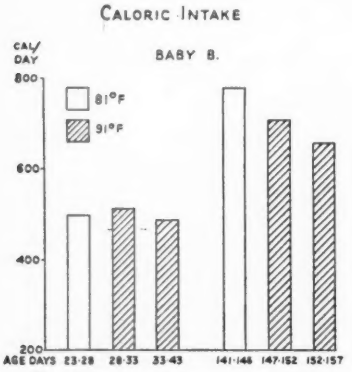


FIG. 3. Increased response to environmental temperature with aging.

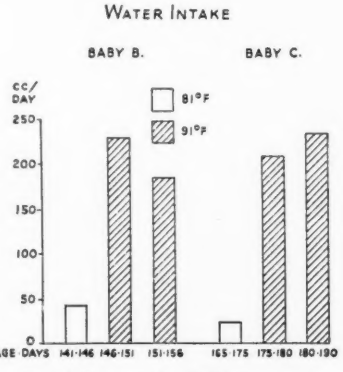


FIG. 4. Increase in distilled water intake with rise in environmental temperature.

were considerably greater with aging (Fig. 6), the neonate varying his water intake practically not at all with a rise in environmental temperature.

The total quantity of fluid ingested, including the boiled water and the water of the milk mixture, did not change with environmental temperature and was remarkably constant except for a gradual increase with increase in body weight. The total fluid intake averaged 1,016 cc. per day at 81° F and 1,013 cc. per day at 91° F. Likewise, the number of feedings per day was not significantly altered by a rise or fall in room temperature.

Posture. The postural changes observed at high room temperature cannot be quantitated and a subjective description must suffice. Within a few hours after exposure to heat stress all the infants, including a two-week-old infant, changed their predominant postures. The arms and legs were extended widely away from the body to increase considerably the surface of the body available for evaporation and radiation.

Figure 7 is a somewhat schematic representation of the postural changes.

The change in total activity with change in temperature was difficult to assess but no consistent alteration in the sleep pattern of these infants was observed. Accurate recording of the duration of sleeping revealed no significant difference at 81° and 91° F.

Discussion

The ad libitum feeding of infants represents a feasible method for the study of the physiological mechanisms regulating food consumption in the human species. Habit and prejudice are poorly developed and, therefore, basic physiological mechanisms can be studied more easily.

The caloric intake of the six infants fed completely ad libitum was remarkably uniform and averaged 120 Calories per kilogram of body weight

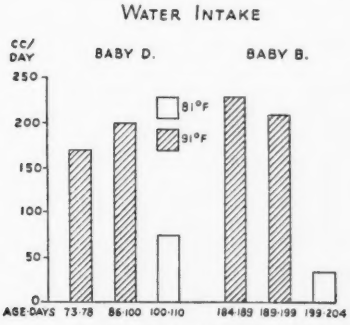


Fig. 5. Decrease in distilled water intake with fall in environmental temperature.

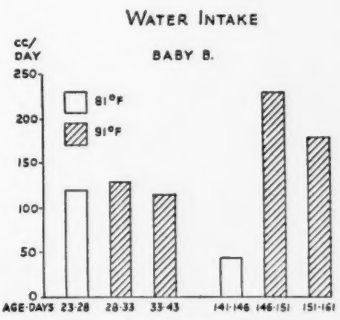


Fig. 6. Increased response to environmental temperature with aging.

at 81° F.—exactly the accepted value for optimal infant nutrition.[9] However, it is obvious from these studies that environmental temperature conditions the feeding behaviour of normal infants, and that the requirements for optimal nutrition must be defined with reference to this temperature. Retardation of growth noted in infants living in the tropics has been attributed in part to a reduced caloric intake.[4]

The physiological mechanisms which bring about this fall in caloric intake with heat stress are unknown. Indeed, the exact mechanisms normally regulating food consumption are the subject of considerable controversy. Gastric motility and the rate of gastric emptying have been considered important factors.[6, 7, 15] However, acute exposure to heat stress without change in body temperature decreased rather than prolonged the gastric emptying time in twelve of seventeen adult subjects studied by Henschel, Taylor, and Keys.[8] Chronic exposure to high environmental temperatures was not studied in this manner by these workers.

Radiographic study of two of our infants revealed no significant difference in gastric motility at 81° F. as compared with 91° F.

Fever has been known for centuries to reduce food intake; however, there was no elevation of rectal temperature at any time in the infants studied. It is probable that the mean body temperature and therefore the resting metabolism was elevated during heat stress because of a diminished gradient between skin and internal organs. This impairment of heat loss from the body may accentuate the thermal responses to the ingestion of food.[1, 14] This factor may be of importance both in these studies and those of Brobeck who demonstrated a marked fall in food intake and activity in the rat accompanying a rise in environmental temperature.[2]

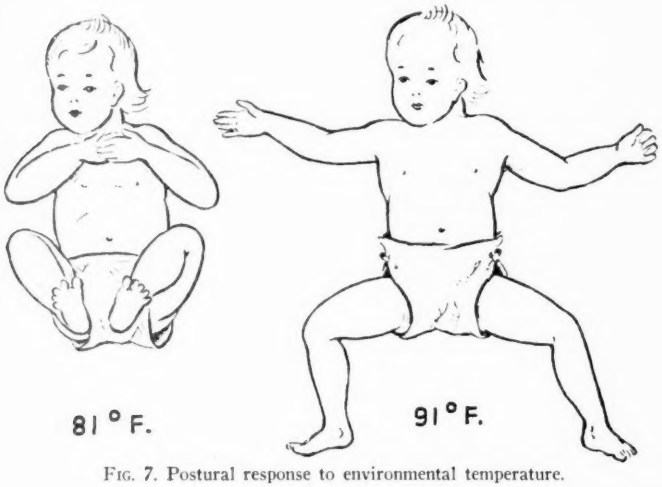


FIG. 7. Postural response to environmental temperature.

The preference of infants for milk rather than water is a well-known observation. However, heat stress induced a significant modification of this preference. Although the total fluid intake as milk and distilled water was not increased on exposure to heat, water alone was substituted for fluid containing protein, fat, electrolyte, and the other constituents of milk. The mechanisms responsible for this substitution are unknown and are certainly not simply thirst mechanisms since both mixtures offered were fluids. However, by this substitution definite physiological gains were obtained in the absence of an increased total fluid intake. The reduction in specific dynamic action attained by a reduction in food intake facilitated the adjustment to heat stress. The concomitant reduction in nitrogen intake lowered the osmotic load for renal excretion and thereby led to water conservation in the presence of increased extrarenal losses by evaporation. The reduction in

chloride and sodium intake tended to prevent excessive electrolyte retention with hyperosmolarity of the body fluids as noted in previous studies[3] and thereby facilitated heat loss from the body. Therefore, a reduction in milk intake during heat stress is equivalent, as regards body economy, to an increase in water intake. The younger infants did not react as markedly in their behavioural adjustment. The two-week-old infant actually increased his intake of milk mixture appreciably at 91° F. After three days of heat stress, obvious pitting edema of the lower extremities was present and a marked gain of weight occurred. The infant was strikingly restless and irritable. It is impossible to determine from these studies whether the increase with age in the substitution of water for milk during heat stress is a result of learned behaviour or maturation of regulating mechanisms. This question could be decided by similar studies using as subjects infants of varying ages who had not been previously exposed to heat stress.

The data obtained from these experiments suggest certain considerations of practical value in the care of infants in summer. Dilute feeding mixtures (50 Calories per 100 cc., for example) should be used during heat stress rather than concentrated milk mixtures supplemented by water offered ad libitum after feedings, as is commonly practised. By the use of a dilute feeding mixture an adequate intake of water in relation to calories, protein, and electrolytes is assured.

Summary and Conclusions

The intake of water and milk mixture on a self-demand basis was measured in 57 periods in six infants under controlled environmental temperatures of 81° and 91° F.

An increase in water intake and fall in milk intake were noted on exposure to heat stress. The converse occurred when the room temperature fell. These reactions were less marked in the younger infants.

Acknowledgment

The author is indebted to Drs. Grover F. Powers, Daniel C. Darrow, and John R. Brobeck for their stimulation and advice in this study.

References

1 Booth, G. and Strang, J. M.: Changes in temperature of the skin following the ingestion of food. Arch. Int. M., 1936, *57*, 531.

2 Brobeck, J. R.: Effects of variations in activity, food intake and environmental temperature on weight gain in the albino rat. Am. J. Physiol., 1945, *143*, 1.

3 Cooke, R. E., Pratt, E. L., and Darrow, D. C.: The metabolic response of infants to heat stress. Yale J. Biol., 1950, *22*, 227.

4 Cluver, E. H.: The problem of ventilation on the Witwatersrand. The Transvaal Medical Journal, 1922.

5 Davis, C. M.: Liberal infant feeding. J. Am. Diet. Ass., 1946, *22*, 602.

6 Frank, L. K.: The newborn as a young mammal with organic capacities, needs and feelings. Psychosom. M., 1945, *7*, 169.

7 Gulliksen, D. P., Fogelberg, A., and Kardos, L.: Anorexia and gastric motility. Am. J. Digest Dis., 1939, *5,* 814.

8 Henschel, A., Taylor, H. L., and Keys, A.: The gastric emptying time of man at high and normal environmental temperatures. Am. J. Physiol., 1944, *141,* 205.

9 Jeans, P. C.: The feeding of healthy infants and children. J. Am. M. Ass., 1942, *120,* 913.

10 Lee, D. H. K.: A basis for the study of man's reaction to tropical climate. Queensland University Papers, 1940, *1,* 1.

11 Ragsdale, A. C., Brody, Samuel, Thompson, J. J., and Worstell, D. M.: Environmental physiology. II. Influence of temperature, 50° to 105° F., on milk production and feed consumption in dairy cattle. Research Bulletin 425. University of Missouri College of Agriculture, 1948.

12 Ragsdale, A. C., Worstell, D. M., Thompson, H. J., and Brody, Samuel: Environmental physiology. VI. Influence of temperature, 50° to 0° F. and 50° to 95° F., on milk production, feed and water consumption and body weight in Jersey and Holstein cows. Research Bulletin 449. University of Missouri College of Agriculture, 1949.

13 Simsarian, F. P. and McLendon, P. A.: Further records of the self demand schedule in infant feeding. J. Pediat., S. Louis, 1945, *27,* 109.

14 Strang, J. M. and McClugage, H. B.: The specific dynamic action of food in abnormal status of nutrition. Am. J. M. Sc., 1931, *182,* 49.

15 Taylor, Rood: Hunger in the infant. Am. J. Dis. Child., 1914, *14,* 233.

16 Thompson, H. J., Worstell, D. M., and Brody, Samuel: Environmental physiology. V. Influence of temperature, 50° to 105° F., on water consumption in dairy cattle. Research Bulletin 436. University of Missouri College of Agriculture, 1949.

17 Trainham, G., Pilafian, G. J., and Kraft, R. M.: A case history of twins breast fed on a self-demand regime. J. Pediat., S. Louis, 1945, *27,* 97.

NEWS AND COMMENT

DEPARTMENT OF PEDIATRICS

VIRGINIA S. GREEN

On July 1, 1927, exactly six years after the establishment of the Department of Pediatrics at Yale University, Dr. Grover F. Powers assumed the chairmanship—a post which he held for twenty-four years. At the present time, the State of Connecticut can point to one of the lowest infant mortality rates in the country and to its number of pediatricians per capita which is as high as in any state. These facts are probably not without some relationship to the vision, wisdom, and inspiration with which Dr. Powers guided his department.

It was Dr. Powers' conviction that exemplary teaching and training require concomitant research activity. Soon after his arrival in 1927, a laboratory of clinical bacteriology was established under the direction of Dr. James D. Trask for the investigation and treatment of infectious diseases. Further researches in the field of metabolic disorders have been carried out under the direction of Dr. Daniel C. Darrow.

Shortly after the return of Dr. Powers, another major development took place in the Department of Pediatrics when the pediatricians began to assume responsibility for babies in the maternity wards. Along with the newborn infant, data accumulated by the obstetrician about the mother during her pregnancy is given over to the pediatrician, so that the association between the two departments is a close one.

At a time when there were few pediatric clinics oriented to the importance of behavioral and emotional problems of children, Dr. Marian C. Putnam, trained in pediatrics, psychiatry, and child development, was assigned to full-time duty on the pediatric service. The establishment of the Rooming-In Project at Yale under Dr. Edith B. Jackson extended the opportunity to study parent-child relationships to the prenatal and neonatal periods. With the appointment of Dr. Milton Senn as Director of the Child Study Center, a further move was made toward integrating these studies with similar studies in later childhood and toward relating pediatrics with psychiatry and sociology in general.

The New Haven Rheumatic Fever and Cardiac Program was established by Dr. Powers in 1947 and is under the directorship of Dr. Ruth Whittemore.

Public relations both locally and nationally have flourished under Dr. Powers' skillful leadership. The Department of Pediatrics has many friends among the physicians in the community. There are professional affiliations with schools, children's centers and homes, and other hospitals.

The Department of Pediatrics has been constantly developing and extending programs for the care of sick children during Dr. Powers' chairmanship, but perhaps of greater importance are the hundreds of medical students, postgraduate students and fellows who received training under Dr. Powers. Scattered throughout the nation are numerous alumni of Yale's Department of Pediatrics filling important posts in the field of medicine. There are ten who are chairmen of university departments of pediatrics, at least three more holding full professorships, and an additional number who hold advanced academic rank. Amongst other alumni are the chairmen of eleven additional pediatric units, over half of these units having affiliations with medical schools. The chief of the Medical Department of

Brookhaven National Laboratory is an alumnus of the Department of Pediatrics. Another former resident and instructor became an assistant director-general of the World Health Organization and is now chief of the U.S. Children's Bureau. The deans of the medical schools of the Universities of Pennsylvania and of Virginia are alumni of Dr. Powers' department. Other alumni include two chiefs of psychiatric units, one professor of microbiology, two chiefs of university school health projects, one head of a university maternal and child health department, one head of radiology, and ten or more who are filling important posts in the field of public health. There have been two associate chiefs in charge of medical affairs of the U.S. Children's Bureau. Of no less importance are the numerous practising pediatricians who received part or all of their training in this department, most of whom are medical leaders in their communities.

Such are the tangible accomplishments engendered by Dr. Powers. But there are other contributions that defy enumeration—those intangible and long-enduring ones which are the true measure of Dr. Powers' success as a teacher, scholar, and personal friend of all who came under his influence.

BIBLIOGRAPHY OF GROVER F. POWERS, M.D.

1920

1. Three probable cases of spinal muscular atrophy of Werdnig-Hoffman type (with J. H. M. Knox, Jr.). Southern M. J., *13,* 86-92.
2. Acrocephaly and scaphocephaly with symmetrically distributed malformations of the extremities; a study of the so-called "acrocephelosyndactylism" (with E. A. Park). Am. J. Dis. Child., *20,* 235-315.

1921

3. The prevention of the development of rickets in rats by sunlight (with P. G. Shipley, E. A. Park, E. V. McCollum, and Nina Simmonds). Proc. Soc. Exp. Biol., N. Y., *19,* 43-47.
4. The prevention of rickets in the rat by means of radiation with the mercury vapor quartz lamp (with E. A. Park, P. G. Shipley, E. V. McCollum, and Nina Simmonds). Proc. Soc. Exp. Biol., N. Y., *19,* 120-121.

1922

5. The prevention of the development of rickets in rats by sunlight; studies on experimental rickets XIV (with E. A. Park, P. G. Shipley, E. V. McCollum and Nina Simmonds). J. Am. M. Ass., *78,* 159-165.
6. Effectiveness of infant welfare clinics from a medical point of view (with J. H. M. Knox, Jr.). J. Am. M. Ass., *78,* 707-710.
7. Study on experimental rickets XIX. The prevention of rickets in the rat by means of radiation with mercury vapor quartz lamp (with E. A. Park, P. G. Shipley, E. V. McCollum, and Nina Simmonds). Bull. Johns Hopk. Hosp., *33,* 125-127.
8. The influence of light and darkness upon the development of xerophthalmia in the rat (with E. A. Park and Nina Simmonds). Proc. Soc. Exp. Biol., N. Y., *20,* 81-84.

1923

9. The influence of radiant energy upon the development of xerophthalmia in rats; a remarkable demonstration of the beneficial influence of sunlight and out-of-door air upon the organism (with E. A. Park and Nina Simmonds). J. Biol. Chem., *55,* 575-597.

10. A proof of the regulatory influence of cod liver oil on calcium and phosphorous metabolism (with E. A. Park and Ruth A. Guy). Am. J. Dis. Child., *26*, 103-111.

1925

11. Tetany as a cause of convulsions in very young infants. J. Am. M. Ass., *84*, 1907-1908.
12. Comparison and interpretation on a caloric basis of the milk mixtures used in infant feeding. Am. J. Dis. Child., *30*, 453-475.
13. Tetany as a cause of convulsions in whooping cough. Am. J. Dis. Child., *30*, 632-641.

1926

14. A comprehensive plan of treatment for the so-called intestinal intoxication of infants. Am. J. Dis. Child., *32*, 232-257.

1932

15. Yale University School of Medicine, Department of Pediatrics. Methods and Prob. M. Educ., 20th ser., publ. Rockefeller Foundation, pp. 53-58.

1933

16. The alleged correlation between the rate of growth of the suckling and the composition of the milk of the species. J. Pediat., S. Louis, *3*, 201-216.

1934

17. Tuberculosis. I. Interpretation of roentgenograms of the chests of children with tuberculosis; a correlation of the roentgenograms of fourteen children with clinical and pathologic data (with Margaret L. Bronson and H. M. Zimmerman). Am. J. Dis. Child., *47*, 104-148.
18. The Pediatric Clinic of the Yale University School of Medicine. J. Pediat., S. Louis, *4*, 671-677.
19. Potency of milks fortified with respect to antirachitic properties; clinical tests and a proposed method of procedure (with Martha M. Eliot). J. Am. M. Ass., *102*, 1823-1824.

1935

20. Infant feeding; historical background and modern practice. J. Am. M. Ass., *105*, 753-761.

1936

21. Bedside teaching; consideration of the patient's emotional response to case discussion (with E. Kahn). J. Am. M. Ass., *107*, 639-641.

1937

22. Blood transfusion as a therapeutic measure. In Brennemann's *Practice of pediatrics*, Hagerstown, Md., W. F. Prior Co., Inc. Vol. I, chapter 14.

1938

23. Remarks on a case of congenital idiopathic hypertrophy of the heart (with P. M. LeCompte). J. Pediat., S. Louis, *13*, 760-771.

1939

24. Developments in pediatrics in the past quarter century. Yale J. Biol., *12*, 1-22.

1941

25. Developments in pediatrics in the past quarter century. Bull. Vancouver M. A., *17*, 162-173.
26. Chemotherapy in the treatment of streptococcus empyema in children. Internat. Clin., *2*, 132-156.

1942

27. Streptococcosis, streptococcal fever, and scarlet fever (an unsigned editorial). Connecticut State M. J., *6*, 118.
28. James Dowling Trask, M.D. (1890-1942). Connecticut State M. J., *6*, 572-574.
29. Streptococcosis in children; nosographic and statistical study (with P. L. Boisvert, D. C. Darrow, and J. D. Trask). Am. J. Dis. Child., *64*, 516-534.

1943

30. Tuberculosis and streptococcosis (with P. L. Boisvert). Yale J. Biol., *15*, 517-530.

1944

31. Dr. James Dowling Trask, 1890-1942. Yale J. Biol., *16*, 395-399.
32. Eczema and hemolytic streptococcal disease in children (with P. L. Boisvert). Yale J. Biol, *16*, 595-612.
33. Age as a factor in streptococcosis (with P. L. Boisvert). J. Pediat., S. Louis, *25*, 481-504.

1945

34. School health problems as seen in a pediatric clinic. Connecticut State M. J., *9*, 11-16., Pub. Health Nursing, *37*, 7-13.

1948

35. Some observations on the feeding of premature infants based on twenty years' experience at the New Haven Hospital. Pediatrics, *1*, 145-158.
36. Humanizing hospital experiences. (Presidential address, American Pediatric Society). Am. J. Dis. Child., *76*, 365-379.

1949

37. Remarks to undergraduate students of clinical medicine. Yale J. Biol., *22*, 109-113.

1950

38. Dr. Winternitz and pediatrics at Yale. Yale J. Biol., *22*, 715-718.

1951

39. The care of premature infants on the University Service, Grace-New Haven Community Hospital (with R. E. Cooke). Yale J. Biol., *23*, 282-287.
40. Sam Harvey: Yankee Surgeon-Philosopher. Yale J. Biol., *23*, 445-449.

YALE UNIVERSITY SCHOOL OF MEDICINE

ALUMNI DAY PROGRAM

Friday, February 22, 1952

GENERAL INFORMATION

Registration: All Alumni are requested to register upon arrival at the Club Room, Sterling Hall of Medicine. This desk will be open at 8:30 a.m., and will close at 6:30 p.m.; it will also serve as a general information center.

There is a registration fee of $2.50 to cover miscellaneous costs. In addition, there is a charge of $3.00 for the luncheon, Club Room, Sterling Hall of Medicine.

To facilitate planning, Alumni are requested to register in advance by mail, and to *reserve their luncheon tickets,* by returning the inclosed card. Luncheon tickets will be mailed if check for $5.50 (registration fee plus luncheon ticket) is received in time; otherwise, tickets may be called for at the registration desk. NOTE: Reservations will be held only until 10:45 a.m., Alumni Day.

Rooms: If any Alumni wish to spend the night in New Haven, either before or after Alumni Day, hotel accommodations will be secured for them.

PROGRAM

8:00 A.M. *Surgical Operative Schedule,* Farnam Operating Rooms

Thoracic Surgery, G. E. Lindskog, M.D., and Staff

Neurosurgery, W. J. German, M.D., and Staff

Cardiovascular Surgery, W. W. L. Glenn, M.D.

Orthopedics, N. M. Shutkin, M.D.

9:30 A.M. *Grand Rounds, Medicine,* Fitkin Amphitheater
J. P. Peters, M.D., and Staff

10:00 A.M. *Obstetrics,* Conference, 3023 Farnam Memorial Building
"The Toxemias of Pregnancy," J. B. Forman, M.D.

10:30 A.M. *Psychiatry,* Demonstration of Observation Rooms, Room 305 Institute of Human Relations
F. C. Redlich, M.D., and Staff

11:00 A.M. *A Symposium, Medical and Surgical Aspects of Cardiovascular Surgery,* Gymnasium, Sterling Hall of Medicine
Chairman, H. M. Marvin, M.D., Associate Clinical Professor of Medicine
W. W. L. Glenn, M.D., Assistant Professor of Surgery
A. V. N. Goodyer, M.D., Assistant Professor of Medicine
F. D. Gray, M.D., Assistant Professor of Medicine
L. J. Hampton, M.D., Associate Professor of Anesthesiology
A. J. Kummer, M.D., Assistant Professor of Radiology
A. A. Liebow, M.D., Professor of Pathology
J. M. White, M.D., Assistant Professor of Pharmacology
Ruth Whittemore, M.D., Associate Clinical Professor of Pediatrics

1:00 P.M. *Lunch for Alumni,* Club Room, Sterling Hall of Medicine
Presiding: C. N. H. Long, M.D., Dean

3:00-4:00 P.M. *Meeting of Yale Alumni in Medicine,* Gymnasium, Sterling Hall of Medicine
Presiding, Charles L. Larkin, M.D., President, Association of Yale Alumni in Medicine
The Medical Student at Yale, John D. Marshall, President of the Student Council
Presentation to Grover F. Powers, M.D., by Daniel C. Darrow, M.D., Professor of Pediatrics
Report to the Alumni, C. N. H. Long, M.D., Dean

4:00-5:00 P.M. *Departmental Open House*

5:00 P.M. *Social Hour,* Club Room, Sterling Hall of Medicine

EVENTS

PHARMACOLOGY SEMINAR

December 6, 1951

THE LIFE-SPAN OF WHITE BLOOD CELLS MEASURED WITH RADIOPHOSPHORUS. By D. L. Kline, Department of Physiological Chemistry, Yale University.

Researchers widely disagree on the length of life of the white blood cells. Studies thus far are really measurements of the replacement time of destroyed or removed white cells by an animal. *In vitro* and *in vivo* work with radioactive phosphorus (P^{32}) indicates that the isotope is incorporated into the DNA of the nucleus only at the time of formation of the cell. Once in the nucleus, the phosphorus is held there for the life of the cell and not exchanged.

In this study the isotope was administered orally to humans, and blood samples were drawn at intervals and analyzed for DNA P^{32}. A curve, showing the isotopic concentration in the white blood cells plotted against time, was similar in shape to that which had been obtained by Shemin and Rittenberg using N^{15} labeled red blood cells. The P^{32} concentration rose slowly for four to five days, sharply climbed, maintained a plateau from the 6th to the 10th day, and fell off in an *S* shape.

The random disappearance of an isotope follows the form of a log curve. If DNA P^{32} had been exchanged during the study, the resultant would have been the typical log curve; this did not occur. Mathematical analysis of the curve indicates that labeled white blood cells disappear from body circulation about 13.3 days after administering the isotope. Since the cells did not appear in large quantities until four to five days after giving the P^{32}, it is possible that they remained at the site of formation for that time.

This method does not distinguish between the types of white blood cells. It appears that the life span of their major components is not a matter of hours, but of days—approximately two weeks.

J. K. R.

YALE MEDICAL SOCIETY

January 9, 1952

DYE INTERMEDIATES AS POTENTIAL CARCINOGENS: CLINICAL AND LABORATORY STUDIES WITH BENZIDINE. By J. Wister Meigs and Louis J. Sciarini.

Although not considered to be true carcinogens, benzidine and its derivatives may produce cancer at the base of the urinary bladder after prolonged exposure. Since it is possible that these substances or their metabolites appear in the urine and so give rise to cancer, metabolites of these dyes are being investigated for carcinogenic activity. Feeding experiments are being conducted on both mice and dogs. Further studies on industrial workers have shown that benzidine penetrates the skin as well as the respiratory epithelium; therefore, daily showers and changes of underclothing are recommended for workers exposed to these potentially hazardous substances.

V. S. G.

INFLUENCE OF HYPOTHALAMIC LESIONS UPON FOOD INTAKE. By Bal K. Anand and John R. Brobeck.

The hypothalamus has been further implicated as a regulatory and integrative region by the demonstration of a "feeding center" in the lateral

hypothalamic region of the diencephalon of the rat. Marked differences in food intake were observed in a series of 94 female rats as a result of lesions placed in various regions of the hypothalamus. Using the Horsley-Clarke apparatus and electric coagulation, bilateral lesions in the medial hypothalamus at the lateral aspect of the ventromedial nucleus produced obesity due to hyperphagia. Overnight food consumption of as much as 40 gm. resulted in extreme cases. Unilateral lesions in this region were ineffective in producing hyperphagia.

As a result of inadvertent bilateral lesions extending well into both lateral hypothalamic regions, a definite hypophagia resulted to the extent that the rats would starve to death despite *ad libitum* feeding conditions. By systematically producing small, selective lesions, the location of the feeding center was determined. The relationship between the ventromedial nucleus and the lateral "feeding center" was determined by creating lesions selectively in these regions. A unilateral "feeding center" lesion did not affect the hyperphagia of the animal previously given bilateral ventromedial nucleus lesions. If this lateral lesion was inflicted on both sides, immediate cessation of food intake resulted. Thus, the ventromedial nucleus may be regulatory of the "feeding center," as evidenced by the lack of inhibition of eating habits when this nucleus was bilaterally destroyed. It seems that eating may be a reflex facilitated by higher centers.

DONALD DEAN DAVIS

FAMILIAL COINCIDENCE OF SICKLING AND THALASSEMIA. By David H. Clement.

A seven-year-old boy, who became extremely ill requiring transfusions, digitalization, and oxygen therapy, and who recovered and remained well for the past two years, showed evidence of sickle cell and Mediterranean anemias. A careful investigation of family history found the sickle cell trait in the father and paternal grandfather and thalassemia minor in his mother and maternal grandmother. The patient is homozygous for neither trait; he is heterozygous for both traits and as such demonstrated the minor forms of both diseases.

Clinical laboratory tests for sickle cell anemia should be made on all patients whose ancestry centers geographically along the northern Mediterranean coast. For accurate results, tests should be conducted with appropriate reducing agents such as ascorbic acid or sodium bisulfite.

In this patient it may be assumed that the diseases are additive, but their precise pathogenesis is obscure.

J. K. R.

TOXICOLOGY SEMINAR

January 14, 1952

THE TRIBULATIONS OF THE INDUSTRIAL TOXICOLOGIST. By D. D. Irish, Biochemical Research Laboratory, Dow Chemical Company, Midland, Michigan.

The work done in the speaker's laboratory has its theoretical basis in comparative biochemistry, i.e., the assumption that every species of living organism has some biochemical difference from every other and therefore that any organism can be eliminated in the presence of any other. Practically, the problem is to discover the toxicological agent that will effect this end at least to a useable degree in that the agent should be able to destroy or at least control the destructive organisms while avoiding injury to man and to most organisms beneficial to man. The scope of the investigations

conducted is extensive, covering insect, plant, microbial, and animal toxicology.

Some of the chief problems involved in this work were discussed. There is the primary problem of insuring the safe use of a product which involves, apart from basic research on toxicity, co-operation with medical and production personnel, and with the sales department in attempts at educating the public in proper use of the material. There is also the very practical problem of having to screen large numbers of new chemicals with relatively few personnel.

Finally, specific cases were discussed where toxicity studies had presented some unusual features relevant to the aforementioned problems. Briefly touched on were studies of styrene, carbon tetrachloride, alkyl halides, silicone compounds, ethylene oxide, and ethylene imine.

R. G.

YALE MEDICAL SOCIETY

Woodward Lecture

January 16, 1952

AUSTRALIAN STUDIES ON TWO MOSQUITO-BORNE VIRUS DISEASES: RABBIT MYXOMATOSIS AND MURRAY VALLEY ENCEPHALITIS. By Sir Macfarlane Burnet, Director, Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia.

In 1951 the Australian government experimentally released the rabbit myxoma virus as a possible means of controlling the excessive rabbit population. In the same year there appeared numerous cases of an often fatal human encephalitis in the Murray Valley, where the rabbit epidemic also was at its peak. A suspected connection between the two diseases initiated the research the results of which Sir Marfarlane presented. These results, however, show that two different viruses account for the two diseases, with one important epidemiological similarity. Both are spread by mosquitos; hence the similar distribution along the river valleys and also the identical seasonal incidence of the diseases. Rabbit myxomatosis has previously been described in Brazil, and further work showed that it is specific for the rabbit (it can, however, be grown on the chorioallantoic membrane of the chick embryo). Seemingly, the disease belongs to the pox group, its virus being similar to vaccinia.

Murray Valley encephalitis, in contrast, belongs to the group of arthropod-borne encephalitides, being not unlike Japanese B and St. Louis encephalitis. Its range of infectivity in animals is identical with that of Japanese B, but it is serologically different. It is believed to be identical with the Australian X-disease, of which two epidemics are known to have occurred in 1917 and in 1918. The seasonal incidence and age distribution of X-disease and Murray Valley encephalitis are almost identical. The reactivation of this disease probably was due to the fact that 1951 was an especially good "mosquito-year" and to some upset having occurred in the bird-mosquito-bird cycle, to which the virus is usually restricted.

N. A. H.

CARDIOVASCULAR STUDY UNIT

January 23, 1952

EXPERIMENTAL ASPECTS OF HYPERTENSION. By Ephraim Schorr, Professor of Medicine, Cornell University School of Medicine, New York, New York.

VEM and VDM are part of the humoral mechanisms responsible for the control of the capillary bed. They exert no direct effect, but seem to act by respectively increasing or decreasing the sensitivity of the precapillary sphincters to epinephrine. Assay for these substances is done on the mesenteric capillaries of the rat, by using serial dilutions of the sera of substances to be tested. Similarly, the conjunctival vessels of man have been used, under direct microscopic observation. VDM has been identified by Dr. Schorr chemically; it it the iron-storing ferritin. This substance itself is stored in the inactive form, and when released by the liver, spleen, or muscle its -SH groups are freed and thus it becomes physiologically active. This process is anerobic, while the inactivation, which can occur in the liver alone, requires the presence of oxygen. VEM in contrast is produced as well as inactivated by the kidney alone, being also restricted to anerobic production and aerobic breakdown.

The relation of these substances to hypertension has been studied in Goldblatt animals. In the stage of rising blood-pressure the VEM is far in excess of VDM; however, when the latter reaches an equivalent level, the blood pressure stops rising. A great increase in the number and size of capillaries accompanies this process. DOCA-produced hypertension does not seem to involve this pathway, since no changes can be demonstrated in the VEM-VDM system or in the capillary bed.

N. A. H.

Back Issues of the Journal Wanted

The Journal needs copies of the following issues to complete back sets and will purchase these issues for one dollar each.

Volume	*Number*	*Volume*	*Number*
1	3, 4, 5	11	5
2	1, 3, 4, 5	14	6
3	3, 4, 5	15	1
4	1, 2	18	3
7	1	20	2, 3, 5, 6
9	1		

—•—

Please send copies of the above issues to

The Yale Journal of Biology and Medicine

333 Cedar Street

New Haven 11, Connecticut

in urinary tract infections:

Prompt therapeutic response has been obtained with Terramycin in chronic pyelonephritis due to E. coli, and resistant to other chemotherapy. Urinary cultures became negative in 24 hours and remained so for a 4 week follow-up period. The clinical result was recorded as "good."

Nesbit, R. M.; Adcock J.; Baum, W. C., and Owen, C. R.: J. Urol. 65:336 (Feb.) 1951.

CRYSTALLINE TERRAMYCIN HYDROCHLORIDE

available | *Capsules, Elixir, Oral Drops, Intravenous, Ophthalmic Ointment, Ophthalmic Solution.*

ANTIBIOTIC DIVISION **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

a coating to calm the colon

Kaopectate controls diarrheal disturbances by threefold action. Kaopectate:

1. coats and protects the irritated intestinal mucosa
2. absorbs and removes bacteria, toxins, and other irritants
3. consolidates the stool to normal consistency

For simple, direct control of common diarrheas . . .

℞ Kaopectate*

Each fluidounce contains:

Kaolin	90 grs.
Pectin	2 grs.

Available in 10 fluidounce bottles

*Trademark, Reg. U.S. Pat. Off.

a product of

Upjohn Research

for medicine . . . produced with care . . . designed for health

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN